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(54) **PRRS VIRUS INDUCING TYPE I INTERFERON IN SUSCEPTIBLE CELLS**

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(58) **Field of Classification Search**

None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to the field of attenuated live viruses useful as vaccine or medicament for preventing or treating Porcine Reproductive and Respiratory Syndrome (PRRS) in swine, and is based on the surprising finding of a PRRS virus which is able to induce the interferon type I response of a cell infected by said virus. In one embodiment, the PRRS virus according to the invention is a PRRS virus mutant comprising, in comparison with the genome of a wild type strain, a mutation in the gene encoding the non structural protein 1 (nsp1) of said virus.

27 Claims, 6 Drawing Sheets

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FIG. 1

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EU LoN94-13 nsp1Beta          SSVYRWKKFVVFTDSSPNGRPRMMWTPESDDSADLEALPPELERQVEILIRSFPAHHPVS 60
delta nsp1 IX-10 nsp1Beta     ....................MM.......................................... 58
delta nsp1 XVII-1 nsp1Beta    ....................MMM......................................... 57
delta nsp1 XVIII-12 nsp1Beta  ....................MMMM........................................ 56
delta nsp1 XIX-2 nsp1Beta     ....................MMMMM....................................... 55
delta nsp1 XX-9 nsp1Beta      ....................MMMMMM...................................... 54

EU LoN94-13 nsp1Beta          LADWELAESPENGFSFSTYHSGGYLVQNPDVFDSKCWLSCFLDQPIEVRLYEDYLANAFG 120
delta nsp1 IX-10 nsp1Beta     ............................................................ 118
delta nsp1 XVII-1 nsp1Beta    ............................................................ 117
delta nsp1 XVIII-12 nsp1Beta  ............................................................ 116
delta nsp1 XIX-2 nsp1Beta     ............................................................ 115
delta nsp1 XX-9 nsp1Beta      ............................................................ 114

EU LoN94-13 nsp1Beta          YQTKWGVSGKYLQRRLQVNGIRAVIDPDGPIHVEALSCPQSWIRHLTLDDDVTPGFVRLT 180
delta nsp1 IX-10 nsp1Beta     ............................................................ 178
delta nsp1 XVII-1 nsp1Beta    ............................................................ 177
delta nsp1 XVIII-12 nsp1Beta  ............................................................ 176
delta nsp1 XIX-2 nsp1Beta     ............................................................ 175
delta nsp1 XX-9 nsp1Beta      ............................................................ 174

EU LoN94-13 nsp1Beta          SLRIVPNTEPTTLRIFRFGAHKWYG 205
delta nsp1 IX-10 nsp1Beta     ........................... 203
delta nsp1 XVII-1 nsp1Beta    ........................... 202
delta nsp1 XVIII-12 nsp1Beta  ........................... 201
delta nsp1 XIX-2 nsp1Beta     ........................... 200
delta nsp1 XX-9 nsp1Beta      ........................... 199
```

FIG. 2

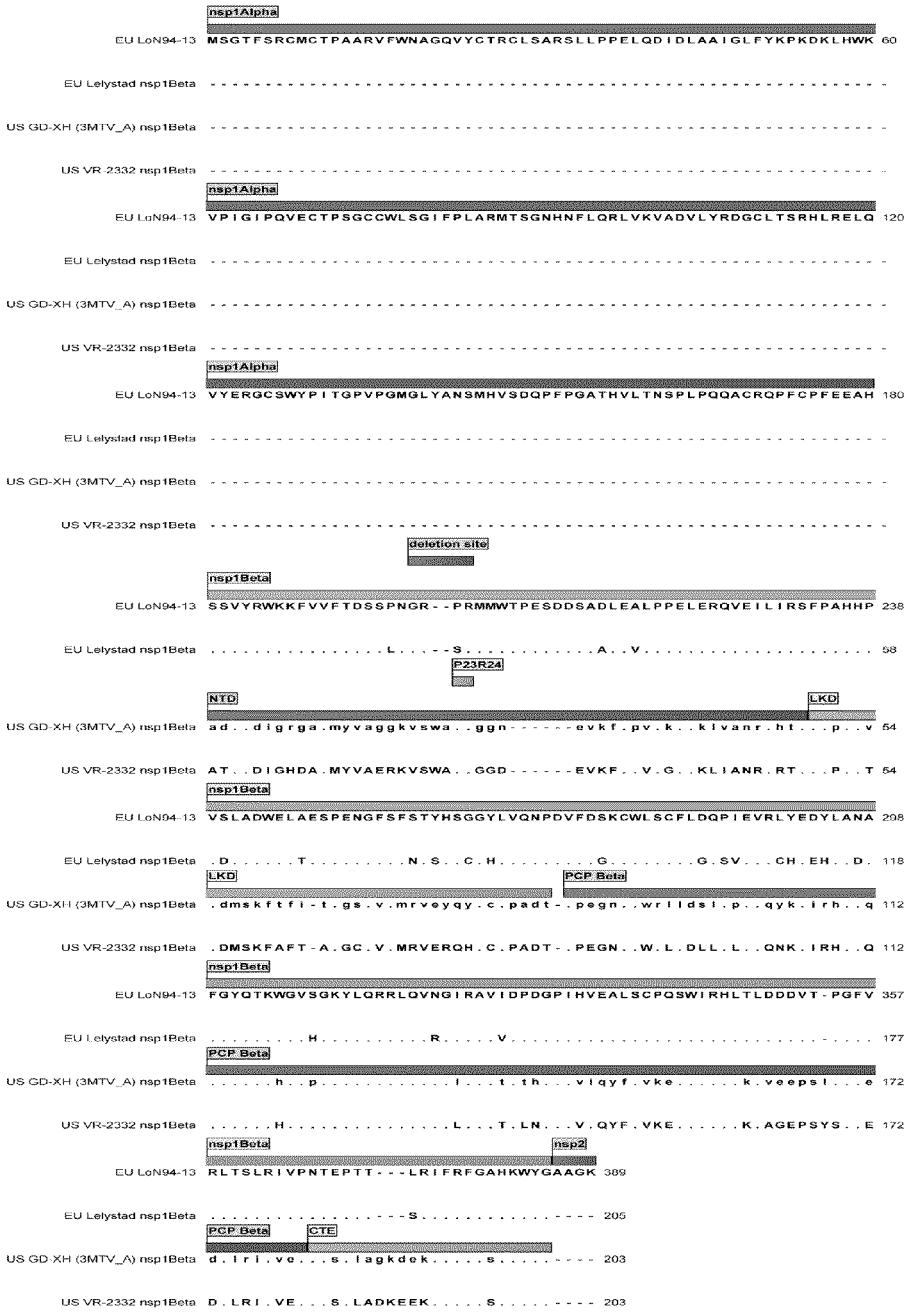

nsp1Alpha
EU LoN94-13 MSGTFSRCMCTPAARVFWNAGQVYCTRCLSARSLLPPELQDIDLAAIGLFYKPKDKLHWK 60
EU Lelystad nsp1Beta
US GD-XH (3MTV_A) nsp1Beta
US VR-2332 nsp1Beta
nsp1Alpha
EU LoN94-13 VPIGIPQVECTPSGCCWLSGIFPLARMTSGNHNFLQRLVKVADVLYRDGCLTSRHLRELQ 120
EU Lelystad nsp1Beta
US GD-XH (3MTV_A) nsp1Beta
US VR-2332 nsp1Beta
nsp1Alpha
EU LoN94-13 VYERGCSWYPITGPVPGMGLYANSMHVSDQPFPGATHVLTNSPLPQQACRQPFCPFEEAH 180
EU Lelystad nsp1Beta
US GD-XH (3MTV_A) nsp1Beta
US VR-2332 nsp1Beta
deletion site
nsp1Beta
EU LoN94-13 SSVYRWKKFVVFTDSSPNGR--PRMMWTPESDDSADLEALPPELERQVEILIRSFPAHHP 238
EU Lelystad nsp1Beta .....L.....-S.....A..V..... 58
P23R24
NTD
LKD
US GD-XH (3MTV_A) nsp1Beta ad..digrga.myvaggkvswa..ggn------evkf.pv.k..klvanr.ht...p..v 54
US VR-2332 nsp1Beta AT..DIGHDA.MYVAERKVSWA..GGD------EVKF..V.G..KLIANR.RT...P..T 54
nsp1Beta
EU LoN94-13 VSLADWELAESPENGFSFSTYHSGGYLVQNPDVFDSKCWLSCFLDQPIEVRLYEDYLANA 298
EU Lelystad nsp1Beta .D.....T.....N.S..C.H.....G.....G.SV...CH.EH..D. 118
LKD
PCP Beta
US GD-XH (3MTV_A) nsp1Beta .dmskftfi-t.gs.v.mrveyqy.c.padt--pegn..wrlldsl.p..qyk.lrh..q 112
US VR-2332 nsp1Beta .DMSKFAFT-A.GC.V.MRVERQH.C.PADT--PEGN..W.L.DLL.L..QNK.IRH..Q 112
nsp1Beta
EU LoN94-13 FGYQTKWGVSGKYLQRRLQVNGIRAVIDPDGPIHVEALSCPQSWIRHLTLDDDVT-PGFV 357
EU Lelystad nsp1Beta .....H.....R.....V..... 177
PCP Beta
US GD-XH (3MTV_A) nsp1Beta .....h..p.....l...t.th...vlqyf.vke.....k.veepsl...e 172
US VR-2332 nsp1Beta .....H.....L...T.LN...V.QYF.VKE.....K.AGEPSYS..E 172
nsp1Beta
nsp2
EU LoN94-13 RLTSLRIVPNTEPTT---LRIFRFGAHKWYGAAGK 389
EU Lelystad nsp1Beta .....-S.....---- 205
PCP Beta
CTE
US GD-XH (3MTV_A) nsp1Beta d.lrl.vc...s.lagkdek.....s.....---- 203
US VR-2332 nsp1Beta D.LRI.VE...S.LADKEEK.....S.....---- 203

FIG. 3A

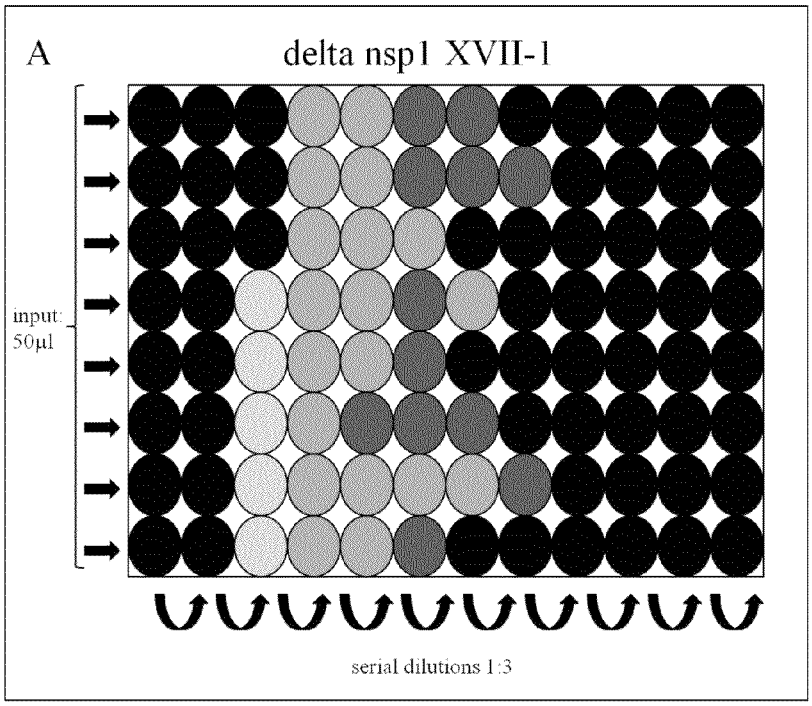

A
delta nsp1 XVII-1
input:
50µl
serial dilutions 1:3

FIG. 3B

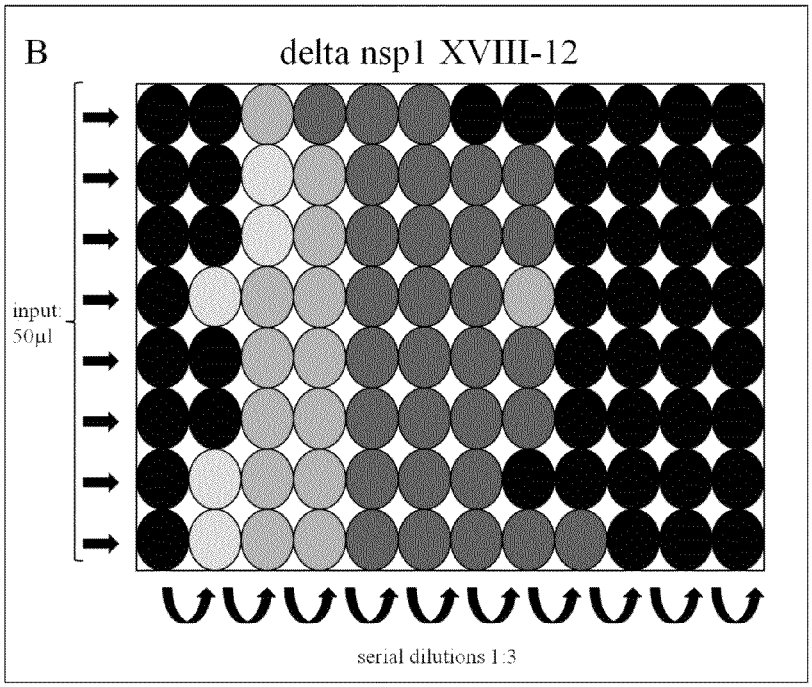

B
delta nsp1 XVIII-12
input:
50µl
serial dilutions 1:3

FIG. 4

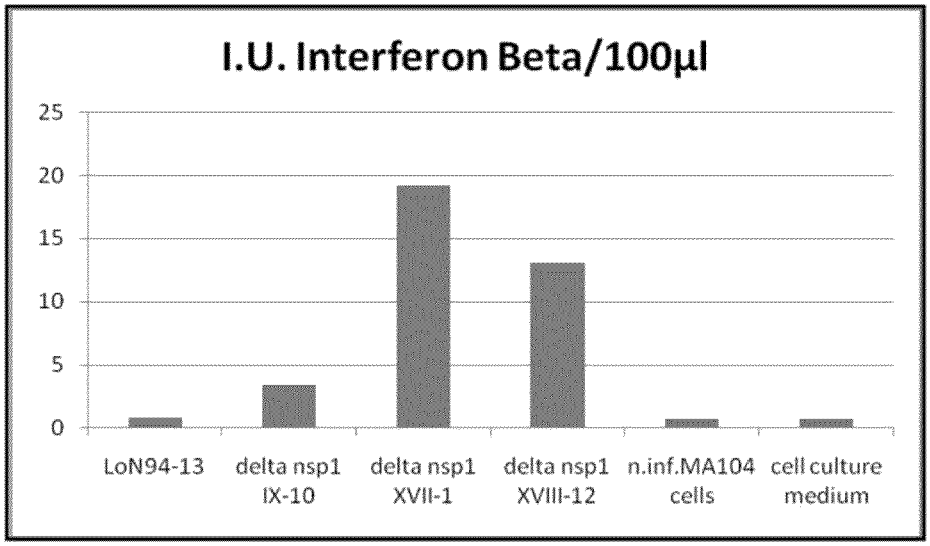

I.U. Interferon Beta/100µl
25
20
15
10
5
0
LoN94-13
delta nsp1 IX-10
delta nsp1 XVII-1
delta nsp1 XVIII-12
n.inf.MA104 cells
cell culture medium

FIG. 5

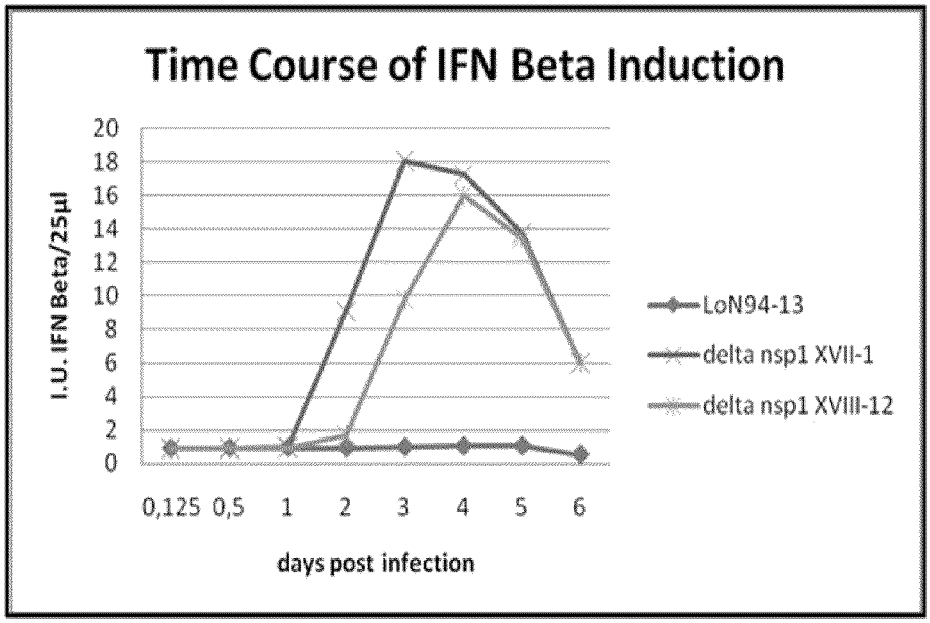

Time Course of IFN Beta Induction
I.U. IFN Beta/25µl
20
18
16
14
12
10
8
6
4
2
0
0,125
0,5
1
2
3
4
5
6
days post infection
LoN94-13
delta nsp1 XVII-1
delta nsp1 XVIII-12

FIG. 6

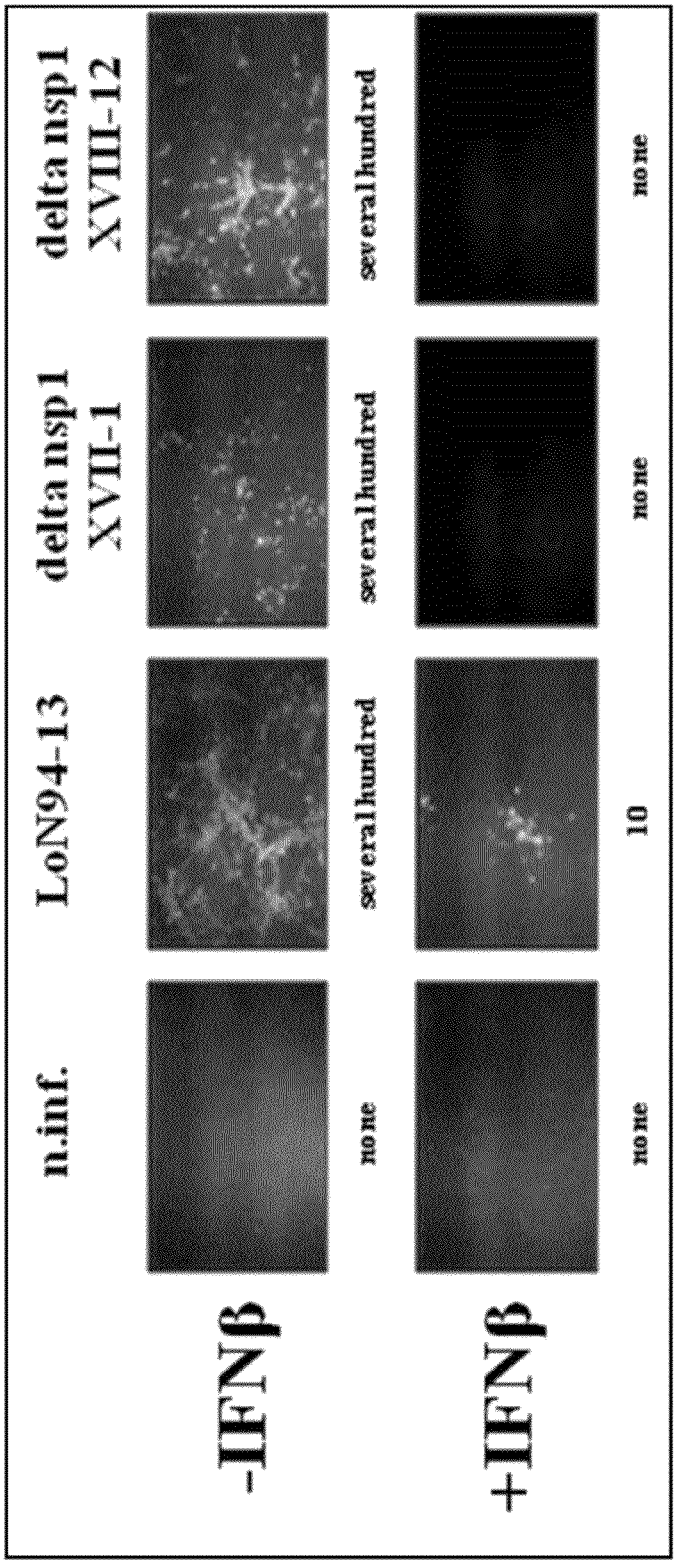
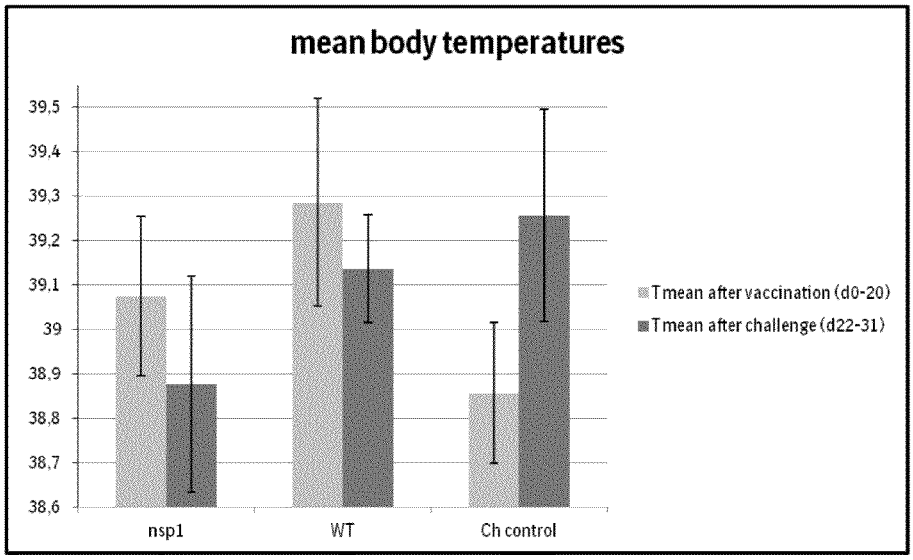

n.inf.
LoN94-13
delta nsp1 XVII-1
delta nsp1 XVIII-12
-IFNβ
+IFNβ
none
several hundred
several hundred
several hundred
none
10
none
none

FIG. 7


mean body temperatures
39,5
39,4
39,3
39,2
39,1
39
38,9
38,8
38,7
38,6
nsp1
WT
Ch control
Tmean after vaccination (d0-20)
Tmean after challenge (d22-31)

PRRS VIRUS INDUCING TYPE I INTERFERON IN SUSCEPTIBLE CELLS

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Sep. 4, 2014 is named 01-2739-US-1-UP-SEQ.txt and is 243,336 bytes in size.

FIELD OF THE INVENTION

The present invention belongs to the field of vaccines and medicaments for the prophylaxis and treatment of infectious diseases. In particular, it relates to attenuated live viruses useful as vaccine or medicament for preventing or treating Porcine Reproductive and Respiratory Syndrome (PRRS), a viral disease affecting swine.

BACKGROUND OF THE INVENTION

Porcine reproductive and respiratory syndrome virus (PRRSV) is a member of the virus family Arteriviridae and belongs, together with the Coronaviridae, to the virus order Nidovirales. PRRSV is an enveloped virus with a single-stranded, positive-sense RNA genome of about 15 kilobases comprising nine open reading frames (ORFs), namely ORF1a, ORF1ab, ORF2a, ORF 2ab, and ORFs 3 through ORF7. ORFs 1a and 1ab encode large polyproteins that are processed into the viral nonstructural proteins (nsp) by auto- and transcleavages of viral proteases nsp1, nsp2, and nsp4 (Snijder and Meulenberg, 1998).

There are two distinct viral PRRSV genotypes causing similar clinical symptoms that diverge by about 40% on nucleotide sequence level, genotype I (EU) and genotype II (US). The North American (US) prototype strain is VR-2332, while the European (EU) prototype strain is Lelystad virus.

PRRSV is considered one of the economically most important infectious agents in pigs causing late-term reproductive failure in sows and respiratory disease in growing pigs. Often, PRRSV infection is complicated by secondary bacterial infections being attributed to the immunosuppressive nature of the virus. Also, PRRSV viremia lasts for weeks, and virus then still can be detected in lymphoid organs for several months, demonstrating difficulties or failure of the host's immune response to clear the virus (Allende et al., 2000).

The specific immune response to PRRSV infection is characterized by delayed induction of neutralizing antibodies (Lopez and Osorio, 2004) and short cell-mediated immune response (Xiao et al., 2004). It is commonly accepted that these effects can in part be attributed, along with presentation of decoy epitopes (Ostrowski et al., 2002; Ansari et al., 2006) and glycan shielding of viral envelope proteins (Ansari et al., 2006), to the viral inhibition of the host's innate immune system. It has been demonstrated that PRRSV infection does not or only weakly or delayedly induce production of type I interferon (IFN) (interferon α and interferon β; (Miller et al., 2004)) or type II IFN, (interferon γ; (Meier et al., 2003)) in susceptible cell lines (swine pulmonary alveolar macrophages, monkey kidney cells MARC-145) and/or pigs (Buddaert et al., 1998).

Thus, there is a need for novel vaccines and medications effecting a rapid induction of neutralizing antibodies and interferon responses for the prophylaxis and treatment of PRRSV infection.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**: Sequence alignment of nsp1β protein sequences from parental EU PRRSV strain LoN94-13 and from vaccine candidates (SEQ ID NOS 7 and 21-25, respectively, in order of appearance).

FIG. **2**: Sequence alignment of nsp1β proteins from PRRSV strains (SEQ ID NOS 82, 8 and 83-84, respectively, in order of appearance).

FIG. **3**: PRRSV-specific immunofluorescence of virus stock titrations. (A) delta nsp1 XVII-1; (B) delta nsp1 XVIII-12. Black, negative fluorescence; light grey, few positive cells; grey, foci of positive cells; dark grey, complete cell monolayer positive.

FIG. **4**: Virus stocks of vaccine candidates contain IFNβ.

FIG. **5**: Time course of IFNβ induction after infection of MA104 cells.

FIG. **6**: Delta nsp1 mutants show increased sensitivity to type I IFN.

FIG. **7**: Mean body temperatures of vaccinated groups before and after challenge.

DETAILED DESCRIPTION

IFNs play an important role in establishing an effective adaptive immune response against viral infections, and many viruses therefore have developed strategies and counteractions against onset of the host's innate immune system (Haller and Weber, 2009). In the interest to identify the anticipated PRRSV IFN antagonist(s), extensive screening analyses based on cell lines stably expressing genes of interest or on cells transfected with protein-expressing plasmids have identified several PRRSV nonstructural proteins (nsps) including nsp1 (see below), nsp2 (Beura et al., 2010; Li et al., 2010), nsp4 (Beura et al., 2010), and nsp11 (Beura et al., 2010; Shi et al., 2011a) to be involved in blocking the induction of type I IFN.

nsp1 is located at the N-terminus of the PRRSV ORF1a-derived polyprotein 1a and is processed into two multifunctional subunits, nsp1α and nsp1β, each of which contains a papain-like cysteine protease (PCP) domain essential for self-release from the viral polyprotein (den Boon et al., 1995; Chen et al., 2010). nsp1α contains an N-terminal zinc-finger domain and the PCPα protease domain, while nsp1β contains PCPβ. For both nsp1 subunits, nsp1α and nsp1β, the three-dimensional crystal structure has been resolved (Sun et al., 2009; Xue et al., 2010). According to these analyses, nsp1β consists of an N-terminal domain (NTD), a linker domain (LKD), the PCP domain (PCP beta), and a C-terminal extension (CTE); (Xue et al., 2010), see FIG. **2**. C-terminal, nsp1β-mediated cleavage of nsp1 from nsp2 occurs at site WYG (SEQ ID NO: 70)/AGR (SEQ ID NO: 71) for PRRSV US strains (Kroese et al., 2008) or is predicted at site WYG (SEQ ID NO: 70)/AAG (SEQ ID NO: 72) for PRRSV EU strains (Chen et al., 2010), while nsp1α/nsp1β cleavage occurs at site ECAM (SEQ ID NO: 73)/AxVYD (SEQ ID NO: 74) for PRRSV US strains or is predicted at site EEAH (SEQ ID NO: 75)/SxVYR (SEQ ID NO: 76) for PRRSV EU strains (Chen et al., 2010).

Several studies on protein level demonstrated to the mechanistic detail that PRRSV nsp1 and/or its autocleavage-derived subunits nsp1α and/or nsp1β inhibit type I IFN production by interfering with IFN transcription (Song et al., 2010; Kim et al., 2010; Chen et al., 2010; Beura et al., 2010). In addition, it has been demonstrated that nsp1β interferes with the cellular response to interferon (interferon signaling); (Chen et al., 2010). Moreover, it was demonstrated that PRRSV infection

inhibits IFNα and/or IFNβ production in PRRSV infected cells in vitro (Kim et al., 2010; Beura et al., 2010), the subcellular localization of nsp1 (subunits) was determined (Song et al., 2010; Chen et al., 2010), and mechanistic aspects of type I IFN inhibition that were obtained by others from single protein expression experiments were confirmed in cells infected with PRRSV (Shi et al., 2010). Finally, a nsp1 mutagenesis study based on nsp1 protein expression investigated effects on viral IFN inhibition (Shi et al., 2011b), showing that mutations that inactivated papain-like cysteine protease activity of nsp1α made nsp1 lose its IFN antagonism activity, whereas mutations that inactivated papain-like cysteine protease activity of nsp1β did not influence the IFN antagonism activity of nsp1.

However, a viable PRRSV strain that induces IFN production and/or does not interfere with IFN signaling after infection of susceptible cells and/or the host, in particular a PRRSV strain comprising a genomic mutation in its nsp1 gene, has not been described yet.

It is thus an aim of the present invention to make available such a viable PRRS virus inducing the IFN response of a cell, in particular of a host cell, wherein said PRRS virus may serve as an effective vaccine or medicament for the prophylaxis or treatment of the Porcine reproductive and respiratory syndrome in swine.

The solution to the above technical problem is achieved by the description and the embodiments characterized in the claims.

Thus, the invention in its different aspects and embodiments is implemented according to the claims.

The invention is based on the surprising finding of a Porcine Reproductive and Respiratory Syndrome (PRRS) virus which is able to induce the interferon type I response of a cell, in particular of a host cell.

Hence, one aspect of the invention concerns a PRRS virus (PRRSV) which is able to induce the interferon type I production and secretion by a cell infected by said virus, wherein the PRRS virus according to the invention in particular is able to induce or induces the interferon type I production and secretion by an interferon competent cell infected by said virus.

As used herein, it is understood that the terms "interferon type I", "IFN type I", "type I interferon" and "type I IFN" are equivalent.

Interferon type I production and secretion by a cell, as described herein, particularly means that interferon type I is made and released by a cell in response to the infection of the PRRS virus according to the invention. In this regard, interferon type I, as mentioned herein, is preferably interferon-α and/or interferon-β.

The infection of a cell by the PRRS virus according to the invention in particular includes attachment of the virus to the cell, entry of the virus into the cell, disassembly of the virion, and preferably replication and transcription of the viral genome, expression of viral proteins, and assembly and release of new infectious viral particles.

The cell, as mentioned herein, is a primary or secondary susceptible cell, preferably a mammalian cell, in particular a porcine or a simian cell, more preferably said cell is a porcine macrophage or a MA-104 cell or a MARC-145 cell or a Vero cell.

It is further understood that the PRRS virus according to the invention is able to induce in vitro and/or in vivo the interferon type I production and secretion by a cell infected by said virus.

Preferably, the PRRS virus according to the invention is a live PRRS virus and/or a modified-live PRRS virus and/or an attenuated PRRS virus.

The term "attenuated PRRS virus", as described herein, is in particular directed to a PRRS virus which is attenuated in vitro and/or in vivo, more particular in susceptible cell lines and/or the host.

The term "host", as used herein, is in particular directed to animals infectable with PRRS virus, in particular swine, more particular pigs, such as domestic pigs.

As mentioned herein, "attenuated" particularly relates to a reduced virulence of a pathogen, in particular of a wild type PRRS virus, wherein "virulence" is understood to be the degree of pathogenicity, and wherein "pathogenicity" is directed to the ability of the pathogen to produce clinical symptoms in the host, such as elevated body temperature.

In particular preferably, the PRRS virus according to the invention has or shows increased sensitivity to type I INF when compared to wild type PRRSV, wherein the term "sensitivity to type I INF" is understood as reduced viral infectivity when IFNβ is present, preferably in a sufficient amount for significantly reducing viral infectivity of wild type PRRSV, in the medium surrounding the virus at the time of infection.

The term "wild type PRRS virus" or "wild type PRRSV", respectively, as used herein, is in particular directed to an infectious pathogenic PRRS virus, which is particularly capable of causing PRRS in swine. In one particular preferred embodiment, the term "wild type PRRS virus" is directed to a PRRS virus whose genome comprises a RNA sequence or consists of a RNA polynucleotide, wherein said RNA sequence or RNA polynucleotide is a RNA copy of a polynucleotide selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15.

In one embodiment, the PRRS virus according to the invention is a PRRS virus mutant, in particular comprising, in comparison with the genome of a wild type PRRSV strain, a mutation in a gene encoding a protein of said virus.

In a preferred embodiment, the PRRS virus according to the invention comprises a mutation in the gene encoding the nsp1 protein of said virus. Thus, the invention preferably concerns a PRRS virus which is able to induce the interferon type I production and secretion by an infected cell as a result of a mutation in the gene encoding the nsp1 protein, wherein said mutation is preferably a mutation as mentioned hereinafter.

Hence, the invention particularly concerns a PRRS virus comprising, in comparison with the genome of a wild type strain, a mutation in the gene encoding the nsp1 protein. Accordingly, the mutation as described herein is preferably a mutation in comparison with the sequence of the corresponding wild type gene encoding the nsp1 protein.

The invention is thus preferably directed to a PRRS virus; in particular a wild type PRRS virus, wherein a mutation, preferably a mutation as mentioned hereinafter, has been implemented in the genome of said virus resulting in a non-natural nsp1 protein or in the lack of nsp1 protein of said virus.

In the context of the invention it is understood, that the mutation as described herein may be implemented to any PRRS virus, such as to a PRRS virus selected from the group consisting of wild type PRRS virus, attenuated PRRS virus, modified-life PRRS virus, PRRS virus mutant and combinations thereof. In one example, the mutation as described herein may be implemented to an attenuated and/or live PRRS virus, for example to a PRRS virus selected from the group of the PRRS virus strains that have been deposited on 27 Oct. 2004 with the European Collection of Cell Cultures

(ECACC), Porton Down, Salisbury, Wiltshire, SP4 OJG, Great Britain, under the Accession Numbers ECACC 04102703, ECACC 04102702, and ECACC 04102704. Hence, the mutation as described herein can be combined with one or more other mutations, preferably one or more other attenuating mutations, in a PRRS virus.

In the context of the invention, the term "PPRRS virus" is in particular equivalent with "PRRS virus strain".

The term "mutation" in the context of the invention is understood as a change in a genomic sequence, in particular in the RNA sequence of a PRRS virus. Since viruses that use RNA as their genetic material have rapid mutation rates, the term "mutation", as mentioned herein, is particularly directed to a genetically engineered change in a genomic sequence, such as by site directed mutagenesis, which in particular results in a virus growing to titers significantly lower than wild type PRRS virus in interferon competent cells and/or in the infected host, when propagated under the same conditions. Moreover, in another preferred embodiment the mutation described herein can also be caused by natural mutation and subsequent isolation of the PRRS virus according to the invention, wherein said isolated virus includes the mutation described herein.

Preferably, the mutation, as described herein, comprises or consists of one or more point mutations and/or one or more genomic deletions and/or one or more insertions.

The term "nsp1 protein", as used herein, is directed to the PRRSV nonstructural protein 1.

The nsp1 protein is preferably a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2 if the PRRS virus according to the invention is a genotype I PRRS virus, or the nsp1 protein is preferably a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with the polypeptide set forth in SEQ ID NO:3 if the PRRS virus according to the invention is a genotype II PRRS virus.

In one aspect, the PRRS virus according to the invention preferably also may comprise a mutation in the gene encoding the nsp1 protein selected from the group consisting of SEQ ID NOs 1-3.

It is hence understood that the PRRS virus according to the invention is a genotype I PRRS virus or a genotype II PRRS virus. It is further understood that the terms "genotype I" and "genotype II" are equivalent to the terms "genotype 1" and "genotype 2" or to the terms "type 1" and "type 2", as frequently used in the literature in the context of PRRSV.

Sequence identity in the context of the invention is understood as being based on pairwise determined similarity between nucleotide or protein sequences. The determination of percent identity between two sequences is preferably accomplished using a mathematical algorithm, in particular the well-known Smith-Waterman algorithm (Smith and Waterman, M. S. (1981) J Mol Biol, 147(1):195-197). For purposes of the present invention, percent sequence identity of an amino acid sequence is determined using the Smith-Waterman homology search algorithm using an affine 6 gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix 62. The Smith-Waterman homology search algorithm is taught in Smith and Waterman (1981) Adv. Appl. Math 2:482-489, herein incorporated by reference. A variant may, for example, differ from the reference nsp1, nsp1α, nsp1β or NTD molecule by as few as 1 to 15 amino acid residues, as few as 1 to 10 amino acid residues, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue. Alternatively, percent identity of a nucleotide sequence is determined using the Smith-Waterman homology search algorithm using a gap open penalty of 25 and a gap extension penalty of 5. Such a determination of sequence identity can be performed using, for example, the DeCypher Hardware Accelerator from TimeLogic Version G, or the sequence identity is determined with the software CLC MAIN WORKBENCH 4.1.1 (CLC BIO).

The term "having 100% sequence identity", as used herein, is understood to be equivalent to the term "being identical".

In another preferred embodiment, the mutation in the PRRS virus according to the invention comprises or consists of one or more point mutations and/or one or more genomic deletions and/or one or more insertions.

In a further preferred embodiment, the PRRS virus according to the invention comprises a mutation in the gene sequences encoding the nsp1α subunit of the nsp1 protein and/or the nsp1β subunit of the nsp1 protein of said virus.

The term "nsp1α", as mentioned herein, is thus directed to the PRRSV nsp1α subunit of the nsp1 protein, and the term "nsp1β", as used herein, is hence directed to the PRRSV nsp1β subunit of the nsp1 protein.

The nsp1α is preferably a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5 if the PRRS virus according to the invention is a genotype I PRRS virus, or the nsp1α is preferably a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with the polypeptide set forth in SEQ ID NO:6 if the PRRS virus according to the invention is a genotype II PRRS virus.

The nsp1β is preferably a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide selected from the group consisting of SEQ ID NO:7 and SEQ ID NO:8 if the PRRS virus according to the invention is a genotype I PRRS virus, or the nsp1β is preferably a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with the polypeptide set forth in SEQ ID NO:9 if the PRRS virus according to the invention is a genotype II PRRS virus.

In a particular preferred embodiment, the PRRS virus according to the invention comprises a mutation in the gene sequence encoding the N-terminal domain (NTD) of the nsp1β of said virus. The term "NTD", as mentioned herein, is thus directed to the N-terminal domain of the PRRSV nsp1β subunit.

The NTD is preferably a polypeptide or has a polypeptide sequence, respectively, having at least 60%, particularly at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide or a polypeptide sequence, respectively, selected from the group consisting of SEQ ID NO:10 and SEQ ID NO:11 if the PRRS virus according to the invention is a genotype I PRRS virus, or the NTD is preferably a polypeptide or has polypeptide sequence, respectively, having at least 60%, particularly at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with the polypeptide or the polypeptide sequence, respectively, set forth in SEQ ID NO:12 if the PRRS virus according to the invention is a genotype II PRRS virus.

In a preferred embodiment, the NTD comprising the mutation has the sequence selected from the group consisting of the sequences

SXXYXXXXXVXFXDXXXXGXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXXGXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

as set forth in SEQ ID NOs:36-41, if the PRRS virus according to the invention is a genotype I PRRS virus, or the NTD comprising the mutation preferably has the sequence selected from the group consisting of the sequences

AXVYDIGXXAVMXVAXXXXSWAGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXXSWGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXXSGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXXGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXGGXXXXFXXXXXXLXLXAXXXXXS,

as set forth in SEQ ID NOs: 42-47, if the PRRS virus according to the invention is a genotype II PRRS virus.

Thus, the PRRS virus according to the invention preferably comprises a gene sequence encoding a NTD selected from the sequences

SXXYXXXXXVXFXDXXXXGXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXXGXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

SXXYXXXXXVXFXDXXMWXXXSXXSXXLEXLPXXLXXXXXXLXRS,

as set forth in SEQ ID NOs:36-41, if the PRRS virus according to the invention is a genotype I PRRS virus, or the PRRS virus according to the invention preferably comprises a gene sequence encoding a NTD selected from the sequences

AXVYDIGXXAVMXVAXXXXSWAGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXXSWGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXXSGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXXGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXXGGXXXXFXXXXXXLXLXAXXXXXS,

AXVYDIGXXAVMXVAXXGGXXXXFXXXXXXLXLXAXXXXXS.

as set forth in SEQ ID NOs: 42-47, if the PRRS virus according to the invention is a genotype II PRRS virus.

In one exemplary embodiment, the NTD comprising the mutation may, for instance, have the sequence selected from the group consisting of the sequences

SSVYRWKKFVVFTDSSXNGRMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSXNGMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSXNMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSXMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSMMWTPESDDSAXLEXLPPELERQVEILIRS,

as set forth in SEQ ID NOs:48-53, if the PRRS virus according to the invention is a genotype I PRRS virus, or the NTD comprising the mutation may, for instance, have the sequence selected from the group consisting of the sequences

ATVYDIGXXAVMYVAXXKVSWAGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKVSWGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKVSGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKVGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXGGXEVKFEXVPXELKLXANRLXTS,

as set forth in SEQ ID NOs: 54-59, if the PRRS virus according to the invention is a genotype II PRRS virus.

Thus, in one exemplary embodiment, the PRRS virus according to the invention may, for instance, comprise a gene sequence encoding a NTD selected from the sequences

SSVYRWKKFVVFTDSSXNGRMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSXNGMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSXNMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSXMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSSMMWTPESDDSAXLEXLPPELERQVEILIRS,

SSVYRWKKFVVFTDSMMWTPESDDSAXLEXLPPELERQVEILIRS,

as set forth in SEQ ID NOs:48-53, if the PRRS virus according to the invention is a genotype I PRRS virus, or the PRRS virus according to the invention may, for instance, comprise a gene sequence encoding a NTD selected from the sequences

ATVYDIGXXAVMYVAXXKVSWAGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKVSWGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKVSGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKVGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXKGGXEVKFEXVPXELKLXANRLXTS,

ATVYDIGXXAVMYVAXXGGXEVKFEXVPXELKLXANRLXTS,

as set forth in SEQ ID NOs: 54-59, if the PRRS virus according to the invention is a genotype II PRRS virus.

It is thus understood that a genotype I PRRS virus, as mentioned herein, is in particular a virus whose genome comprises a gene sequence coding for a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4,

SEQ ID NO:5, SEQ ID NO:7 and SEQ ID NO:8, or is in particular a virus whose genome comprises a gene sequence coding for a polypeptide having at least 60%, particularly at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide selected from the group consisting of SEQ ID NO:10 and SEQ ID NO:11.

Preferably, the genotype I PRRS virus, as mentioned herein, comprises or consists of a RNA polynucleotide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a RNA polynucleotide complementary to a polynucleotide selected from the group consisting of SEQ ID NO: 13 and SEQ ID NO: 14.

It is further understood that a genotype II PRRS virus, as mentioned herein, is in particular a virus whose genome comprises a gene sequence coding for a polypeptide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a polypeptide selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6 and SEQ ID NO:9, or is in particular a virus whose genome comprises a gene sequence coding for a polypeptide having at least 60%, particularly at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with the polypeptide set forth in SEQ ID NO:12.

Preferably, the genotype II PRRS virus, as mentioned herein, comprises or consists of a RNA polynucleotide having at least 70%, preferably at least 80%, more preferably at least 90%, still more preferably at least 95% or in particular 100% sequence identity with a RNA polynucleotide complementary to the polynucleotide set forth in SEQ ID NO: 15.

In the following, the single letter code for amino acids is used for amino acid sequences, where additionally X signifies any genetically encoded amino acid residue.

Within the context of the invention it is in particular understood that the N-terminal domain (NTD) of nsp1β starts with the N-terminus of nsp1β, preferably starts with the amino acid sequence SXXY (SEQ ID NO: 60) if the PRRS virus is a genotype I PRRS virus or with the amino acid sequence AXVY (SEQ ID NO: 61) if the PRRS virus is a genotype II PRRS virus, and the NTD ends with the serine residue (S) within the amino sequence SFP of the nsp1β. Regarding the NTD domain of a genotype II PRRS virus it is in particular referred to the publication Xue et al. 2010, hereby incorporated by reference. Said amino acid sequences SXXY (SEQ ID NO: 60) or AXVY (SEQ ID NO: 61) and SFP (SEQ ID NO: 62) are especially conserved in the nsp1β of wild type PRRS viruses and are thus preferably used amino acid sequence motifs for defining the NTD domain according to the invention.

In a particular preferred embodiment, the PRRS virus according to the invention thus comprises a mutation in the gene sequence coding for the NTD, wherein the NTD preferably starts with motif SXXY (SEQ ID NO: 60) for PRRS virus type 1 strains or with motif AXVY (SEQ ID NO: 61) for PRRS virus type 2 strains and ends with the serine residue (S) within the conserved SFP (SEQ ID NO: 62) motif of the nsp1β subunit.

According to the invention, it is in particular preferred if said mutation is located within the part of the gene sequence coding for the NTD, where the amino acid stretches folding into β sheet secondary structures are encoded.

In one preferred aspect, the mutation, as described herein, thus comprises a deletion or replacement of a nucleotide triplet coding for an amino acid residue located within the first 24 N-terminal amino acid residues of the NTD sequence.

In particular, it is preferred if the mutation described herein comprises of a deletion or replacement of 2 to 7 or more, preferably consecutive, nucleotide triplets each coding for an amino acid residue located within the first 24 N-terminal amino acid residues of the NTD sequence.

In another preferred aspect, the mutation, as mentioned herein, comprises the deletion or replacement of a nucleotide triplet coding for an amino acid residue with a charged, preferably positively charged, side chain, in particular coding for an arginine residue.

Exemplarily, the mutation mentioned herein preferably consists of a deletion of 2, 3, 4, 5, 6 or 7 consecutive nucleotide triplets coding for the respective number (2, 3, 4, 5, 6 or 7) of consecutive amino acid residues located within the first 24 N-terminal amino acid residues of the NTD sequence, wherein this mutation comprises the deletion of a nucleotide triplet coding for an amino acid residue with a charged, preferably positively charged, side chain, in particular coding for an arginine residue.

The mutation, as described herein, preferably comprises or consists of a deletion or replacement of the nucleotide triplet coding for the first arginine residue (R) located at least 21 amino acid residues in C-terminal direction from the N-terminal amino acid residue of the nsp1β NTD and/or the mutation, as mentioned herein, comprises a deletion or replacement of the nucleotide triplet coding for the arginine residue (R) of the nsp1 amino acid sequence RXMW (SEQ ID NO: 63) if the PRRS virus is a genotype I PRRS virus or with the amino acid sequence RGG (SEQ ID NO: 64) of said virus if the PRRS virus is a genotype II PRRS virus and/or the mutation, as mentioned herein, comprises or consists of a deletion or replacement of the nucleotide triplet coding for the arginine residue (R) of the amino acid sequence RMM (SEQ ID NO: 65) or RGG (SEQ ID NO: 64) of the nsp1 protein.

According to the invention, the phrase "replacement of a nucleotide triplet" is understood as being a replacement of a nucleotide triplet of the wild type sequence by another nucleotide triplet coding for a different amino acid residue than the wild type sequence.

The phrase "deletion of nucleotide triplet" in the context of the invention is directed to a deletion of a nucleotide triplet resulting in the deletion of an amino acid residue in comparison with the wild type sequence.

In particular, said mutation further comprises a deletion or replacement of one nucleotide triplet coding for the amino acid residue flanking said arginine residue (R) in N-terminal direction, wherein said mutation preferably comprises or consists of a deletion or replacement of two consecutive nucleotide triplets coding for the amino acid residues PR (SEQ ID NO: 77).

More particular, said mutation further comprises a deletion or replacement of two, three, four, five, six, seven or more consecutive nucleotide triplets coding for two, three, four, five, six, seven or more amino acid residues flanking said arginine residue (R) in N-terminal direction.

Preferably, said mutation comprises a deletion or replacement of three consecutive nucleotide triplets coding for the amino acid sequence RXR (SEQ ID NO: 66) or APR (SEQ ID NO: 67) of the nsp1β, or wherein said mutation comprises a deletion or replacement of four consecutive nucleotide triplets coding for the amino acid residues GRXR (SEQ ID NO: 68) or WAPR (SEQ ID NO: 69) of the nsp1β.

As result, the PRRS virus according to the invention comprises in one embodiment a gene coding for a nsp1 protein selected from the group consisting of SEQ ID NO:16, SEQ ID

NO:17, SEQ ID NO:18, SEQ ID NO:19 and SEQ ID NO:20, or comprises in another embodiment a gene sequence coding for a nsp1β selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24 and SEQ ID NO:25, or comprises in a further embodiment a gene sequence coding for a NTD selected from the group consisting of SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29 and SEQ ID NO:30.

In yet another preferred embodiment, the mutation, as described herein comprises a deletion of the gene sequence encoding the (whole) nsp1 protein, encoding the (whole) nsp1α subunit, encoding the (whole) nsp1β subunit, or encoding a part, preferably at least seven consecutive amino acid residues, of or the (whole) NTD domain of the nsp1β subunit.

Yet another aspect of the invention is directed to a polynucleotide comprising or consisting of the genome of the PPRS virus according to the invention.

Further, the invention is also directed to a virus particle, wherein said virus particle comprises a polynucleotide which comprises or consists of the genome of the PPRS virus according to the invention or which comprises or consists of a DNA copy of the PPRS virus according to the invention.

Still further, the present invention provides a DNA-Vector comprising a copy of, or a cDNA sequence complementary to, respectively, a polynucleotide which comprises or consists of the genome of the PPRS virus according to the invention.

In one exemplary and non-limiting example the DNA vector, as mentioned herein, comprises a polynucleotide sequence selected from the group consisting of SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34 and SEQ ID NO:35.

Also, the present invention provides a cell comprising a polynucleotide, which comprises or consists of the genome of the PPRS virus according to the invention or which comprises or consists of a DNA copy of the PPRS virus according to the invention.

In one exemplary and non-limiting example the PRRS virus according to the invention, or the genome of the PRRS virus according to the invention, respectively, comprises a RNA sequence or consists of a RNA polynucleotide, wherein said RNA sequence or RNA polynucleotide is a RNA copy of a polynucleotide selected from the group consisting of SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35.

Another aspect of the invention concerns the PRRS virus according to the invention for use as vaccine or medicament, in particular for use in the prophylaxis or treatment of Porcine Reproductive and Respiratory Syndrome preferably in swine. The present invention further provides a composition containing the PRRS virus according to the invention for use as a vaccine or as a medicament, in particular for use in the prophylaxis or treatment of Porcine Reproductive and Respiratory Syndrome preferably in swine.

In a preferred aspect, said vaccine or medicament is administered in two doses or preferably in one dose to an animal in need thereof. By the term "prophylaxis or therapy", as mentioned herein, it is meant that the prophylaxis is to administer a drug, in particular a vaccine, before exposure to PRRSV and the treatment is to administer a drug, in particular a medicament, after infection with PRRSV or onset of PRRS.

In particular, the vaccine, as mentioned herein, is a live vaccine and/or a modified live vaccine and/or an attenuated live or attenuated modified live vaccine.

The strains of the PRRS virus according to the invention can be grown and harvested by methods known in the art, e.g. by propagating in suitable cells like the simian cell line MA-104, Vero cells, or porcine alveolar macrophages. Preferably, vaccines according to the present invention are modified live vaccines comprising one or more of these strains alive in a suitable carrier, but inactivated virus may also be used to prepare killed vaccine (KV). Modified live vaccines (MLV) are typically formulated to allow administration of 10^1 to 10^7 viral particles per dose, preferably 10^3 to 10^6 particles per dose, more preferably 10^4 to 10^6 particles per dose (4.0-6.0 $\log_{10}$ $TCID_{50}$). KV may be formulated based on a pre-inactivation titre of 10^3 to 10^{10} viral particles per dose. The vaccine may comprise a pharmaceutically acceptable carrier, for example a physiological salt-solution. The vaccine may or may not comprise an adjuvant. A suitable adjuvant may optionally also be used. For example, a suitable adjuvant that may be used a-tocopherol acetate which may be obtained under the trade name Diluvac Forte®. Alternatively, alum based adjuvants may be used.

A further aspect of the invention is thus directed to the use of the PRRS virus according to the invention for the preparation of a vaccine or medicament for the prophylaxis or treatment of Porcine Reproductive and Respiratory Syndrome, preferably in swine.

A vaccine according to the present invention may be presented in form of a freeze-dried preparation of the live virus, to be reconstituted with a solvent, to result in a solution for injection. The solvent may, for example, be water, physiological saline, a buffer, or an adjuvanting solvent. The solvent may additionally use adjuvants, for example a-tocopherol acetate. The reconstituted vaccine may then be injected into a pig, for example as an intramuscular or intradermal injection into the neck. For intramuscular injection, a volume of 2 ml may be applied, for an intradermal injection it is typically 0.2 ml. In a further aspect, the present invention therefore is a product, comprising in separate containers a freeze-dried composition of the virus, and a solvent for reconstitution, and optionally further containing a leaflet or label comprising instructions of use.

Yet another aspect of the invention thus concerns a method for the prophylaxis or treatment of Porcine Reproductive and Respiratory Syndrome comprising administering the PRRS virus according to the invention to an animal, preferably to a swine, more preferably to a pig, in particular preferably to a piglet or a sow.

A vaccine according to the present invention may not only comprise the PRRS virus according to the invention as antigen, but may include further components active against PRRS or other porcine viral or bacterial diseases, like porcine circovirus, classical swine fever virus or mycoplasma hyorhinis. Therefore, the invention further relates to a vaccine as described, characterized in that it contains at least one further antigen active against a porcine disease which is not PRRS.

Still another aspect of the invention thus concerns a medicament or vaccine comprising the PRRS virus according to the invention.

Still a further aspect of the invention is directed to a method of preparing a vaccine or medicament, in particular for the prophylaxis or treatment of Porcine Reproductive and Respiratory Syndrome preferably in swine, said method comprising the cultivation of the PRRS virus according to the invention in cell culture.

Moreover, the invention comprises a method of producing the PRRS virus according to the invention, said method comprising the mutagenesis of the gene coding for the nsp1 protein in the genome of a PRRS virus, and wherein the mutation, as described herein, is in particular introduced by genetic engineering in the genome of said virus, preferably by site directed mutagenesis.

Preferably, for any of the aforementioned methods, the above-mentioned DNA-vector is used and/or said methods comprise the detection of interferon type I, in particular interferon type I secretion, and/or of mRNA coding for interferon type I. Said detection in particular comprises the detection of interferon type I and/or of mRNA coding for interferon type I by a bioassay, wherein said bioassay is preferably selected from the group consisting of ELISA, PCR, GLISA, IFA, biosensoric measurement, Surface Plasmon Resonance (SPR) measurement, selective media, lateral flow, biochip measurement, immunomagnetic separation, electrochemiluminescence, chromogenic media, immunodiffusion, DNA hybridization, staining, colorimetric detection, luminescence, and combinations thereof.

In yet a further aspect, the invention provides an immunogenic composition containing the PRRS virus according to the invention.

As used herein, the term "immunogenic composition" in particular refers to a composition that will elicit an immune response in an animal that has been exposed to the composition. An immune response may include induction of antibodies and/or induction of a T-cell response.

Usually, an "immune response" includes but is not limited to one or more of the following effects: the production or activation of antibodies, B cells, helper T cells, suppressor T cells, and/or cytotoxic T cells, directed specifically to an antigen or antigens included in the composition or vaccine of interest. Preferably, the host will display either a therapeutic or a protective immunological (memory) response such that resistance to new infection will be enhanced and/or the clinical severity of the disease reduced. Such protection will be demonstrated by either a reduction in number or severity of, or lack of one or more of the symptoms associated with the infection of the pathogen, in the delay of onset of viremia, in a reduced viral persistence, in a reduction of the overall viral load and/or in a reduction of viral excretion. Thus, an "immune response" in particular means but is not limited to the development in a subset of a cellular and/or antibody-mediated immune response to the composition or vaccine of interest.

In one aspect, the immunogenic composition of the invention is preferably a vaccine or medicament.

As used herein, the term "viremia" is particularly understood as a condition in which PRRS virus particles circulate in the bloodstream of an animal.

The term "animal", as mentioned herein, is in particular directed to swine, more particular to a pig, preferably a domestic pig.

In a preferred aspect, the immunogenic composition of the invention comprises an amount of 10^1 to 10^7 viral particles of the PRRS virus according to the invention per dose, preferably 10^3 to 10^6 particles per dose, more preferably 10^4 to 10^6 particles per dose.

In another preferred aspect, the immunogenic composition of the invention comprises an amount of the PRRS virus according to the invention which is equivalent to a virus titre of at least about 10^3 $TCID_{50}$/mL per dose, preferably between 10^3 to 10^5 $TCID_{50}$/mL per dose

In yet another preferred aspect, the immunogenic composition of the invention further contains one or more pharmaceutically acceptable carriers or excipients. Said one or more pharmaceutically acceptable carriers or excipients are preferably selected from the group consisting of solvents, dispersion media, adjuvants, stabilizing agents, diluents, preservatives, antibacterial and antifungal agents, isotonic agents, and adsorption delaying agents.

The present invention is further directed to the immunogenic composition of the invention for use in a method for

- inducing an immune response against PRRSV, or
- the prevention or reduction of PRRS, or
- the prevention or reduction of PRRSV viremia and/or
- preventing or reducing clinical symptoms, in particular the elevated body temperature, associated with PRRSV infection, or
- the prevention or reduction of the elevated body temperature associated with the administration of an attenuated PRRSV vaccine to an animal.

As used herein, the term "inducing an immune response" to an antigen or composition is the development of a humoral and/or cellular immune response in an animal to an antigen present in the composition of interest.

The term "prevention" or "reduction" or "preventing" or "reducing", respectively, as used herein, means, but is not limited to a process which includes the administration of a PRRSV antigen, namely of the PRRSV according to the invention which is included in the composition of the invention, to an animal, wherein said PRRSV antigen, when administered to said animal elicits or is able to elicit an immune response in said animal against PRRSV. Altogether, such treatment results in reduction of the clinical symptoms of PRRS or of symptoms associated with PRRSV infection, respectively. More specifically, the term "prevention" or "preventing, as used herein, means generally a process of prophylaxis in which an animal is exposed to the immunogenic composition of the present invention prior to the induction or onset of the disease process (PRRS).

Herein, "reduction of PRRS" or "reduction of clinical symptoms associated with PRRSV infection" means, but is not limited to, reducing the number of infected subjects in a group, reducing or eliminating the number of subjects exhibiting clinical symptoms of infection, or reducing the severity of any clinical symptoms that are present in the subjects, in comparison to wild-type infection. For example, it should refer to any reduction of pathogen load, pathogen shedding, reduction in pathogen transmission, or reduction of any clinical sign symptomatic of PRRSV infection, in particular of elevated body temperature. Preferably these clinical symptoms are reduced in subjects receiving the composition of the present invention by at least 10% in comparison to subjects not receiving the composition and may become infected. More preferably, clinical symptoms are reduced in subjects receiving the composition of the present invention by at least 20%, preferably by at least 30%, more preferably by at least 40%, and even more preferably by at least 50%.

Also, the elevated body temperature usually associated with the administration of an attenuated PRRSV vaccine to an animal is reduced in subjects receiving the composition of the present invention by at least 10% in comparison to subjects receiving a conventional attenuated PRRSV vaccine. More preferably, the elevated body temperature usually associated with the administration of an attenuated PRRSV vaccine is reduced in subjects receiving the composition of the present invention by at least 20%, preferably by at least 30%, more preferably by at least 40%, and even more preferably by at least 50%.

Hence, a further advantage of the PRRS virus according to the invention is in particular the effect that its administration to an animal, e.g. for the prophylaxis or treatment of PRRS, results in a reduced increase of body temperature in the animal in comparison with a conventional attenuated PPRSV vaccine.

The term "conventional attenuated PRRSV vaccine", as mentioned herein, is in particular directed to any attenuated

PRRSV useful as a vaccine, wherein said PRRSV does not have the characteristic features of the PRRS virus of the present invention, in particular is not able to induce the interferon type I production and secretion by a cell infected by said PRRSV.

The term "subject", as mentioned herein, in particular relates to an animal.

The term "body temperature", as used herein, in particular refers to the approximate average normal, internal temperature of an animal, for example about 38.5-39° C. in pigs, whereas the body temperature associated with a PRRSV infection may be elevated up to 41° C. in pigs.

The term "reduction of PRRSV viremia" means, but is not limited to, the reduction of PRRS virus entering the bloodstream of an animal, wherein the viremia level, i.e. the number of PRRSV RNA copies per mL of blood serum or the number of plaque forming colonies per deciliter of blood serum, is reduced in the blood serum of subjects receiving the composition of the present invention by at least 50% in comparison to subjects not receiving the composition and may become infected. More preferably the viremia level is reduced in subjects receiving the composition of the present invention by at least 90%, preferably by at least 99.9%, more preferably by at least 99.99%, and even more preferably by at least 99.999%.

The present invention further relates to the use of the PRRS virus according to the invention or of the immunogenic composition of the invention for the preparation of a vaccine or medicament for

inducing an immune response against PRRSV, or
treating or preventing PRRS, or
preventing or reducing PRRSV viremia and/or
preventing or reducing clinical symptoms, in particular the elevated body temperature, associated with PRRSV infection, or
the prevention or reduction of the elevated body temperature associated with the administration of an attenuated PRRSV vaccine to an animal.

In particular, it is preferred if the vaccine or medicament, as mentioned herein, is to be administered in two doses or preferably in a single dose to an animal.

The present invention also provides a method of preparing an immunogenic composition, preferably a vaccine or medicament, more preferably a vaccine or medicament for

inducing an immune response against PRRSV, or
treating or preventing PRRS, or
preventing or reducing PRRSV viremia and/or
preventing or reducing clinical symptoms, in particular the elevated body temperature, associated with PRRSV infection, or
the prevention or reduction of the elevated body temperature associated with the administration of an attenuated PRRSV vaccine to an animal,

wherein said method comprises the step of mixing the PRRS virus according to the invention with one or more pharmaceutically acceptable carriers or excipients, and wherein said one or more pharmaceutically acceptable carriers or excipients are preferably selected from the group consisting of solvents, dispersion media, adjuvants, stabilizing agents, diluents, preservatives, antibacterial and antifungal agents, isotonic agents, and adsorption delaying agents.

In another aspect, the present invention further provides a method for

inducing an immune response against PRRSV, or
treating or preventing PRRS, or
preventing or reducing PRRSV viremia and/or
preventing or reducing clinical symptoms, in particular the elevated body temperature, associated with PRRSV infection, or
the prevention or reduction of the elevated body temperature associated with the administration of an attenuated PRRSV vaccine to an animal,

wherein said method comprises the step of administering the immunogenic composition of the invention to an animal in need thereof, and wherein preferably the immunogenic composition and/or the vaccine is administered in two doses or, more preferably, in a single dose.

EXAMPLES

In the examples five viable, genetically designed PRRSV mutant strains are described which are based on infectious EU PRRSV cDNA clone LoN94-13. These strains, delta nsp1 IX-10, delta nsp1 XVII-1, delta nsp1 XVIII-12, delta nsp1 XIX-2 and delta nsp1 XX-9 (henceforth referred to as vaccine candidates), harbor genomic deletions of two, three, four, five, or six codons in their predicted nsp1 genes, respectively, resulting in deletions of two (motif P21R22 (SEQ ID NO: 77)), three (motif R20P21R22 (SEQ ID NO: 78)), four (motif G19R20P21R22 (SEQ ID NO: 79)), five (motif N18G19R20P21R22 (SEQ ID NO: 80)), or six (motif (P17N18G19R20P21R22 (SEQ ID NO: 81)) amino acids in their predicted nsp1β proteins, respectively (FIG. **1**).

Based on sequence alignments of parental strain LoN94-13 with PRRSV US and EU reference strains VR-2332 and Lelystad virus as well as with strain GD-XH, the deletions are located in the predicted nsp1β portion of nsp1 (FIG. **2**). In more detail, the deletion site for all vaccine candidates is located in the N-terminal domain (NTD) of nsp1β and overlaps with amino acids P23R24 (SEQ ID NO: 77) of GD-XH nsp1β; (FIG. **2**).

After transfection of synthetic transcripts of the vaccine candidates into BHK21 cells and transfer of cell culture supernatant from transfected BHK21 cells onto PRRSV-susceptible MA104 cells, plaque formation typical for PRRSV infection occurred. PRRSV-specificity and viability for each of the vaccine strains then was demonstrated by subsequent cell culture passages on MA104 cells and PRRSV-specific immunofluorescence using monoclonal antibody SDOW17 (Rural Technologies).

After endpoint dilution and generation of virus stocks each derived from material of a single virus plaque, virus titers of the obtained virus stocks were determined for each vaccine candidate by serial virus titrations on 96-well plates containing MA104 cells followed by PRRSV-specific immunofluorescence analyses six to seven days post infection. Unlike experience with titrations of virus stocks from parental PRRSV LoN94-13, the first serial dilutions of vaccine candidates delta nsp1 XVII-1 and delta nsp1 XVIII-12 did not demonstrate a cytopathic effect and virus plaque formation, while at higher dilutions of the virus stocks a cytopathic effect was detectable. Moreover, when respective titrations were investigated by immunofluorescence, cell culture wells of the first serial dilutions were negative for PRRSV infection for both vaccine candidates, while wells infected with higher dilutions of the virus stocks showed PRRSV-specific immunofluorescence, respectively (FIG. **3**).

To determine whether the prepared vaccine candidate virus stocks contained type I IFN, a commercial ELISA specific for human IFNβ (Invitrogen) was used. MA104 cells are epithelial Green Monkey kidney cells. According to the ELISA manufacturer, this Invitrogen ELISA is also suited for the detection of primate IFNβ other than human. For each vac-

cine candidate's virus stock, 100 μl served as assay input, while a virus stock from parental strain LoN94-13, cell culture medium, and medium from noninfected cells served as controls. For quantification of the obtained results, a calibration curve was included using a positive control of the ELISA manufacturer. All samples were measured in duplicates. Unlike the negative controls, virus stocks of the vaccine candidates contained considerable levels of type I IFN, while the virus stock of the parental virus showed IFN levels as low as the negative controls (FIG. **4**).

To confirm the results obtained and to assess kinetics of type I IFN production in cells infected with the vaccine candidates, a time course experiment was performed using MA104 cells infected at a multiplicity of infection (MOI) of 0.001, respectively. Parental strain LoN94-13 served as negative control. While there were only very little and unaltered levels of type I IFN near background detectable for infection with parental strain LoN94-13, vaccine candidates delta nsp1 XVII-1 and delta nsp1 XVIII-12 induced considerable and increasing amounts of up to about 18 I.U. IFNβ per 25 μl sample volume from two days post infection on (FIG. **5**).

It was experimentally assessed whether vaccine candidates containing genomic deletions in nsp1 demonstrate an increased sensitivity to type I IFN (FIG. **6**). 5×10^5 MA104 cells were seeded into a well of a six-well plate and were either not infected (n.inf.) or infected with 800 infectious virus particles of one of the virus strains given on top, respectively. Cells then were either inoculated with 120 I.U. human IFNβ (+IFNβ, bottom row), respectively, or not (−IFNβ, top row). Three days post infection, immunofluorescence analysis specific for the PRRSV capsid protein was performed using monoclonal antibody SDOW17 (Rural Technologies). The total numbers of foci of PRRSV-infected cells per well are given below, respectively.

This experiment demonstrated that inoculation with type I IFN reduced the number of PRRSV infection events in cells after inoculation with a defined number of infectious virus particles, reflecting reduced viral infectivity of PRRSV when IFN was added. This reduction was 80-fold for wild type virus LoN94-13 (FIG. **6**). In addition, for infection with wild type virus, foci of infected cells were smaller than in the well not inoculated with IFN (FIG. **6**). However, for vaccine strains delta nsp1 XVII-1 and delta nsp1 XVIII-12, viral infectivity was reduced to zero when INF was added (FIG. **6**). Thus, these vaccine candidates not only induce production of type I IFN in infected cells (FIG. **4** and FIG. **5**), but also demonstrate increased sensitivity to type I INF when compared to wild type PRRSV (FIG. **6**). This is reflected by their dramatically reduced viral infectivity when IFNβ is present.

Interestingly, the cells infected for the time course experiment summarized in FIG. **5** not only produced considerable amounts of IFNβ, but at the end of the experiment at six days post infection, cells infected with vaccine candidates delta nsp1 XVII-1 and delta nsp1 XVIII-12 showed signs of recovery from usually lytical PRRSV infection. While cells infected with parental strain LoN94-13 were fully lysed, cells infected with the vaccine candidates grew in a partially (delta nsp1 XVIII-12) or completely intact monolayer (delta nsp1 XVII-1). For the latter, only weak signs of a PRRSV-induced cytopathic effect were still detectable. Thus, the interferon production of infected cells together with the observed sensitivity of vaccine candidates to type I IFN correlated with partial or almost complete recovery of infected cells over time. It is reasonable to expect that type I IFN induction by the vaccine candidates together with their increased sensitivity to type I IFN will contribute to a significantly attenuated viral phenotype in the natural host. In particular, expected features of the vaccine candidates' attenuation in pigs include stimulation of the innate and specific immunity, both humoral and cellular, and less shedding and/or shortened viremia of the vaccine viruses.

To assess whether the PRRSV vaccine candidates are attenuated in the host, an animal experiment in piglets was performed.

Three groups, each of ten animals, were infected at study day 0 either with wild-type parental EU PRRSV strain Lon94-13 (WT group), or with delta nsp1 XVIII-12 (nsp1 group), or were not infected (Ch control group). Infection was applied by intramuscular injection to the neck at dosages of $10^{6,56}$ $TCID_{50}$ for LoN94-13 or $10^{6,6}$ $TCID_{50}$ for delta nsp1 XVIII-12, respectively. 21 days post vaccination, all animals were challenged with a virulent EU PRRSV strain being heterologous to LoN94-13 by intramuscular injection and intranasal inoculation at a total dosage of $3\times10^{6,52}$ $TCID_{50}$. Animals were kept until the end of the experiment at day 31, ten days after challenge, and body temperatures were measured for all animals at days 0 (1 and 4 hours post vaccination), 1, 3, 5, 8, 10, 12, 14, 18, 20, 22, 24, 26, 28, and 31.

Mean body temperatures were determined for each animal for the time after vaccination but before challenge using measured body temperature data from all timepoints from day 0 through day 20. Subsequently, mean body temperatures were determined for each group (FIG. **7**, (left-hand) columns). Error bars indicate standard deviations, respectively. Following the same procedure, mean body temperatures and standard deviations were determined for all groups for the time after challenge using measured body temperature data from all timepoints from day 22 through 31 (FIG. **7**, (right-hand) columns).

The term "Significant(ly)" in the context of the following means either (i) p-values of 0.05 or lower as determined by the Dunnett test and obtained from comparing the nsp1 group with either the WT or the Ch control group for either of the two time periods investigated (before and after challenge) or (ii) p-values of 0.05 or lower when comparing the mean temperature change within a group and between the two time periods investigated (before and after challenge).

When comparing the determined mean body temperatures for the time after vaccination but before challenge (left hand columns) in between the three groups, animals from the WT group demonstrated a rise in body temperature of more than 0.4° C. when compared to animals from the noninfected Ch control group, thus demonstrating virulence of LoN94-13 in the infected host. In contrast, the nsp1 group showed a significant reduction in mean body temperature of more than 0.2° C. when compared to the WT group. Thus, since vaccination dosages were the same for the WT and the nsp1 group, the considerable reduction in increase of body temperature compared to WT demonstrates that the described mutation in the genome of delta nsp1 XVIII-12 has significantly reduced virulence of the WT parental strain LoN94-13 in the infected animal.

The significant rise in the mean body temperature of the Ch control group from before challenge to after challenge of 0.4° C. demonstrates virulence of the heterologous EU PRRSV challenge strain. The mean temperature of the WT group after challenge was slightly lower than before challenge, but not significantly reduced (FIG. **7**). In contrast, the mean body temperature of the nsp1 group after challenge was significantly reduced by almost 0.2° C. when compared to that before challenge. Moreover, the body temperature of the nsp1 group after challenge was significantly reduced by almost 0.4° C. when compared to the Ch control group after challenge. Also, mean body temperature of the nsp1 group after

challenge was significantly lower that that of the WT group after challenge by more than 0.2° C. Taken together, this demonstrates that a measurable and significant degree of protection from signs of disease induced by the applied challenge virus was conferred to pigs by vaccination with delta nsp1 XVIII-12. Since parental PRRSV strain LoN94-13 did not confer significant protection, it is evident that the described mutation in the genome of delta nsp1 XVIII-12 is causative for the observed significant protective technical effect.

Analogous experiments, wherein the vaccination was performed with lower amounts (10^5 $TCID_{50}$) of delta nsp1 XVIII-12 showed results similar to the above described results (data not shown). Thus, in practice, a preferred amount of 10^3 to 10^5 $TCID_{50}$ is sufficient for vaccination.

Taken together, the invention described here represents the first known viable PRRSV (EU) strains that contain mutations (deletions) in the nsp1 gene (nsp1β) that induce type I IFN (IFNβ) production in susceptible cells (MA104) and that show increased sensitivity to type I IFN (IFNβ). Moreover, the animal data demonstrates that (i) vaccine candidate delta nsp1 XVIII-12 is significantly attenuated in the host when compared to its parental PRRSV strain LoN94-13 and that (ii) vaccine candidate delta nsp1 XVIII-12 confers significant protection from signs of disease induced by challenge with a heterologous PRRSV strain while parental strain LoN94-13 does not. Thus, the described vaccine candidates or the described mutations therein, either alone or combined with other attenuating mutations, may serve as promising life attenuated PRRSV vaccines.

IN THE SEQUENCE LISTING

SEQ ID NO: 1 corresponds to LoN94-13 complete nsp1 protein,

SEQ ID NO: 2 corresponds to Lelystad virus complete nsp1 protein,

SEQ ID NO: 3 corresponds to VR2332 complete nsp1 protein,

SEQ ID NO: 4 corresponds to LoN94-13 complete nsp1 Alpha,

SEQ ID NO: 5 corresponds to Lelystad virus complete nsp1 Alpha,

SEQ ID NO: 6 corresponds to VR2332 complete nsp1 Alpha,

SEQ ID NO: 7 corresponds to LoN94-13 complete nsp1 Beta,

SEQ ID NO: 8 corresponds to Lelystad virus complete nsp1 Beta,

SEQ ID NO: 9 corresponds to VR2332 complete nsp1 Beta,

SEQ ID NO: 10 corresponds to LoN94-13 nsp1 Beta NTD,

SEQ ID NO: 11 corresponds to Lelystad virus nsp1 Beta NTD,

SEQ ID NO: 12 corresponds to VR2332 nsp1 Beta NTD,

SEQ ID NO: 13 corresponds to LoN94-13 complete viral cDNA insert,

SEQ ID NO: 14 corresponds to Lelystad virus complete genome,

SEQ ID NO: 15 corresponds to VR2332 complete genome,

SEQ ID NO: 16 corresponds to delta nsp1 IX-10 complete nsp1 protein sequence,

SEQ ID NO: 17 corresponds to delta nsp1 XVII-1 complete nsp1 protein sequence,

SEQ ID NO: 18 corresponds to delta nsp1 XVIII-12 complete nsp1 protein sequence,

SEQ ID NO: 19 corresponds to delta nsp1 XIX-2 complete nsp1 protein sequence,

SEQ ID NO: 20 corresponds to delta nsp1 XX-9 complete nsp1 protein sequence,

SEQ ID NO: 21 corresponds to delta nsp1 IX-10 complete nsp1Beta protein sequence,

SEQ ID NO: 22 corresponds to delta nsp1 XVII-1 complete nsp1Beta protein sequence,

SEQ ID NO: 23 corresponds to delta nsp1 XVIII-12 complete nsp1Beta protein sequence,

SEQ ID NO: 24 corresponds to delta nsp1 XIX-2 complete nsp1Beta protein sequence,

SEQ ID NO: 25 corresponds to delta nsp1 XX-9 complete nsp1Beta protein sequence,

SEQ ID NO: 26 corresponds to delta nsp1 IX-10 nsp1Beta NTD protein sequence,

SEQ ID NO: 27 corresponds to delta nsp1 XVII-1 nsp1Beta NTD protein sequence,

SEQ ID NO: 28 corresponds to delta nsp1 XVIII-12 nsp1Beta NTD protein sequence,

SEQ ID NO: 29 corresponds to delta nsp1 XIX-2 nsp1Beta NTD protein sequence,

SEQ ID NO: 30 corresponds to delta nsp1 XX-9 nsp1Beta NTD protein sequence,

SEQ ID NO: 31 corresponds to delta nsp1 IX-10 complete viral cDNA insert sequence,

SEQ ID NO: 32 corresponds to delta nsp1 XVII-1 complete viral cDNA insert sequence,

SEQ ID NO: 33 corresponds to delta nsp1 XVIII-12 complete viral cDNA insert sequence,

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SEQ ID NO: 36 corresponds to a (type 1) nsp1 Beta NTD with mutation (deletion of 2 aa),

SEQ ID NO: 37 corresponds to a (type 1) nsp1 Beta NTD with mutation (deletion of 3 aa),

SEQ ID NO: 38 corresponds to a (type 1) nsp1 Beta NTD with mutation (deletion of 4 aa),

SEQ ID NO: 39 corresponds to a (type 1) nsp1 Beta NTD with mutation (deletion of 5 aa),

SEQ ID NO: 40 corresponds to a (type 1) nsp1 Beta NTD with mutation (deletion of 6 aa),

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SEQ ID NO: 55 corresponds to a (type 2) nsp1 Beta NTD with mutation (deletion of 3 aa),

SEQ ID NO: 56 corresponds to a (type 2) nsp1 Beta NTD with mutation (deletion of 4 aa),

SEQ ID NO: 57 corresponds to a (type 2) nsp1 Beta NTD with mutation (deletion of 5 aa),

SEQ ID NO: 58 corresponds to a (type 2) nsp1 Beta NTD with mutation (deletion of 6 aa),

SEQ ID NO: 59 corresponds to a (type 2) nsp1 Beta NTD with mutation (deletion of 7 aa).

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SEQUENCE LISTING

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Gln Val Glu Ile Leu Ile Arg Ser Phe Pro Ala His His Pro Val Ser
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    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Ala
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Val Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
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Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Ala
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Pro Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Asn Trp
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Gln Val Glu Ile Leu Ile Arg Ser Phe Pro Ala His His Pro Val Asp
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Asp Gly Lys Cys Trp Leu Ser Cys Phe Leu Gly Gln Ser Val Glu Val
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Trp Gly Val His Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Arg Gly
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Leu Phe Tyr Arg Pro Glu Glu Pro Leu Arg Trp Thr Leu Pro Arg Ala
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Phe Pro Thr Val Glu Cys Ser Pro Ala Gly Ala Cys Trp Leu Ser Ala
65                  70                  75                  80

Ile Phe Pro Ile Ala Arg Met Thr Ser Gly Asn Leu Asn Phe Gln Gln
                85                  90                  95

Arg Met Ile Arg Val Ala Ala Glu Leu Tyr Arg Ala Gly Gln Leu Thr
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Pro Ala Val Leu Lys Ala Leu Gln Val Tyr Glu Arg Gly Cys Arg Trp
        115                 120                 125

Tyr Pro Ile Val Gly Pro Ala Pro Gly Val Ala Val Tyr Ala Asn Ser
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Tyr Val Ala Glu Arg Lys Ile Ser Trp Ala Pro Arg Gly Gly Asp Glu
        195                 200                 205

Val Lys Phe Glu Ala Val Pro Gly Glu Leu Arg Leu Ile Ala Asn Arg
    210                 215                 220

Leu Arg Thr Ser Phe Pro Pro His His Thr Val Asp Met Ser Lys Phe
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Ala Phe Thr Ala Pro Gly Cys Gly Val Ser Met Arg Val Glu Arg Gln
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His Gly Cys Leu Pro Ala Asp Thr Val Pro Glu Gly Asn Cys Trp Trp
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Ser Leu Phe Asp Ser Leu Pro Leu Glu Val Gln Asn Lys Glu Ile Arg
        275                 280                 285

His Ala Asn Gln Phe Gly Tyr Gln Thr Lys His Gly Val Ser Gly Lys
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Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Leu Arg Ala Val Thr Asp
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Leu Asn Gly Pro Ile Val Val Gln Tyr Phe Ser Val Lys Glu Ser Trp
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Ile Arg His Leu Lys Leu Ala Gly Glu Pro Ser Tyr Ser Gly Phe Glu
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Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
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Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
                85                  90                  95

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            100                 105                 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
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Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
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        35                  40                  45

Leu Phe Tyr Lys Pro Arg Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Ala
65                  70                  75                  80

Val Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
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                85                  90                  95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Ala
            100                 105                 110

Pro Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Asn Trp
        115                 120                 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Phe Ala Asn Ser
    130                 135                 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His
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<210> SEQ ID NO 6
<211> LENGTH: 180
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 6

Met Ser Gly Ile Leu Asp Arg Cys Thr Cys Thr Pro Asn Ala Arg Val
1               5                   10                  15

Phe Met Ala Glu Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
            20                  25                  30

Ser Leu Leu Pro Leu Asn Leu Gln Val Ser Glu Leu Gly Val Leu Gly
        35                  40                  45

Leu Phe Tyr Arg Pro Glu Glu Pro Leu Arg Trp Thr Leu Pro Arg Ala
    50                  55                  60

Phe Pro Thr Val Glu Cys Ser Pro Ala Gly Ala Cys Trp Leu Ser Ala
65                  70                  75                  80

Ile Phe Pro Ile Ala Arg Met Thr Ser Gly Asn Leu Asn Phe Gln Gln
                85                  90                  95

Arg Met Val Arg Val Ala Ala Glu Leu Tyr Arg Ala Gly Gln Leu Thr
            100                 105                 110

Pro Ala Val Leu Lys Ala Leu Gln Val Tyr Glu Arg Gly Cys Arg Trp
        115                 120                 125

Tyr Pro Ile Val Gly Pro Val Pro Gly Val Ala Val Phe Ala Asn Ser
    130                 135                 140

Leu His Val Ser Asp Lys Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Leu Pro Leu Pro Gln Arg Pro Lys Pro Glu Asp Phe Cys Pro Phe
                165                 170                 175

Glu Cys Ala Met
            180


<210> SEQ ID NO 7
<211> LENGTH: 205
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 7

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Asn Gly Arg Pro Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser
            20                  25                  30

Ala Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile
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        35                  40                  45

Leu Ile Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp
    50                  55                  60

Glu Leu Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His
65                  70                  75                  80

Ser Gly Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys
                85                  90                  95

Trp Leu Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu
            100                 105                 110

Asp Tyr Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser
        115                 120                 125

Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val
    130                 135                 140

Ile Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln
145                 150                 155                 160

Ser Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe
                165                 170                 175

Val Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr
            180                 185                 190

Leu Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
        195                 200                 205


<210> SEQ ID NO 8
<211> LENGTH: 205
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 8

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Leu Asn Gly Arg Ser Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser
            20                  25                  30

Ala Ala Leu Glu Val Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile
        35                  40                  45

Leu Ile Arg Ser Phe Pro Ala His His Pro Val Asp Leu Ala Asp Trp
    50                  55                  60

Glu Leu Thr Glu Ser Pro Glu Asn Gly Phe Ser Phe Asn Thr Ser His
65                  70                  75                  80

Ser Cys Gly His Leu Val Gln Asn Pro Asp Val Phe Asp Gly Lys Cys
                85                  90                  95

Trp Leu Ser Cys Phe Leu Gly Gln Ser Val Glu Val Arg Cys His Glu
            100                 105                 110

Glu His Leu Ala Asp Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val His
        115                 120                 125

Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Arg Gly Ile Arg Ala Val
    130                 135                 140

Val Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln
145                 150                 155                 160

Ser Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe
                165                 170                 175

Val Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr
            180                 185                 190

Ser Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
        195                 200                 205
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<210> SEQ ID NO 9
<211> LENGTH: 203
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 9

Ala Thr Val Tyr Asp Ile Gly His Asp Ala Val Met Tyr Val Ala Glu
1 5 10 15

Arg Lys Ile Ser Trp Ala Pro Arg Gly Gly Asp Glu Val Lys Phe Glu
20 25 30

Ala Val Pro Gly Glu Leu Arg Leu Ile Ala Asn Arg Leu Arg Thr Ser
35 40 45

Phe Pro Pro His His Thr Val Asp Met Ser Lys Phe Ala Phe Thr Ala
50 55 60

Pro Gly Cys Gly Val Ser Met Arg Val Glu Arg Gln His Gly Cys Leu
65 70 75 80

Pro Ala Asp Thr Val Pro Glu Gly Asn Cys Trp Trp Ser Leu Phe Asp
85 90 95

Ser Leu Pro Leu Glu Val Gln Asn Lys Glu Ile Arg His Ala Asn Gln
100 105 110

Phe Gly Tyr Gln Thr Lys His Gly Val Ser Gly Lys Tyr Leu Gln Arg
115 120 125

Arg Leu Gln Val Asn Gly Leu Arg Ala Val Thr Asp Leu Asn Gly Pro
130 135 140

Ile Val Val Gln Tyr Phe Ser Val Lys Glu Ser Trp Ile Arg His Leu
145 150 155 160

Lys Leu Ala Gly Glu Pro Ser Tyr Ser Gly Phe Glu Asp Leu Leu Arg
165 170 175

Ile Arg Val Glu Pro Asn Thr Ser Pro Leu Ala Asp Lys Glu Glu Lys
180 185 190

Ile Phe Arg Phe Gly Ser His Lys Trp Tyr Gly
195 200

<210> SEQ ID NO 10
<211> LENGTH: 52
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 10

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1 5 10 15

Pro Asn Gly Arg Pro Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser
20 25 30

Ala Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile
35 40 45

Leu Ile Arg Ser
50

<210> SEQ ID NO 11
<211> LENGTH: 52
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 11

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1 5 10 15

Leu Asn Gly Arg Ser Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser

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            20                  25                  30

Ala Ala Leu Glu Val Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile
        35                  40                  45

Leu Ile Arg Ser
    50


<210> SEQ ID NO 12
<211> LENGTH: 48
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 12

Ala Thr Val Tyr Asp Ile Gly His Asp Ala Val Met Tyr Val Ala Glu
1               5                   10                  15

Arg Lys Ile Ser Trp Ala Pro Arg Gly Gly Asp Glu Val Lys Phe Glu
            20                  25                  30

Ala Val Pro Gly Glu Leu Arg Leu Ile Ala Asn Arg Leu Arg Thr Ser
        35                  40                  45


<210> SEQ ID NO 13
<211> LENGTH: 15116
<212> TYPE: DNA
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 13

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<210> SEQ ID NO 16
<211> LENGTH: 383
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 16

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Met Ser Gly Thr Phe Ser Arg Cys Met Cys Thr Pro Ala Ala Arg Val
1               5                   10                  15

Phe Trp Asn Ala Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
            20                  25                  30

Ser Leu Leu Pro Pro Glu Leu Gln Asp Ile Asp Leu Ala Ala Ile Gly
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        35                  40                  45

Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
65                  70                  75                  80

Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
                85                  90                  95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Thr
            100                 105                 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
        115                 120                 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
    130                 135                 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe
            180                 185                 190

Thr Asp Ser Ser Pro Asn Gly Arg Met Met Trp Thr Pro Glu Ser Asp
        195                 200                 205

Asp Ser Ala Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val
    210                 215                 220

Glu Ile Leu Ile Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala
225                 230                 235                 240

Asp Trp Glu Leu Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr
                245                 250                 255

Tyr His Ser Gly Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser
            260                 265                 270

Lys Cys Trp Leu Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu
        275                 280                 285

Tyr Glu Asp Tyr Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly
    290                 295                 300

Val Ser Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg
305                 310                 315                 320

Ala Val Ile Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys
                325                 330                 335

Pro Gln Ser Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro
            340                 345                 350

Gly Phe Val Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro
        355                 360                 365

Thr Thr Leu Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
    370                 375                 380


<210> SEQ ID NO 17
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 17

Met Ser Gly Thr Phe Ser Arg Cys Met Cys Thr Pro Ala Ala Arg Val
1               5                   10                  15

Phe Trp Asn Ala Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
            20                  25                  30
```

```
Ser Leu Leu Pro Pro Glu Leu Gln Asp Ile Asp Leu Ala Ala Ile Gly
        35                  40                  45

Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
65                  70                  75                  80

Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
                85                  90                  95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Thr
            100                 105                 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
        115                 120                 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
    130                 135                 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe
            180                 185                 190

Thr Asp Ser Ser Pro Asn Gly Met Met Trp Thr Pro Glu Ser Asp Asp
        195                 200                 205

Ser Ala Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu
    210                 215                 220

Ile Leu Ile Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp
225                 230                 235                 240

Trp Glu Leu Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr
                245                 250                 255

His Ser Gly Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys
            260                 265                 270

Cys Trp Leu Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr
        275                 280                 285

Glu Asp Tyr Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val
    290                 295                 300

Ser Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala
305                 310                 315                 320

Val Ile Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro
                325                 330                 335

Gln Ser Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly
            340                 345                 350

Phe Val Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr
        355                 360                 365

Thr Leu Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
    370                 375                 380


<210> SEQ ID NO 18
<211> LENGTH: 381
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 18

Met Ser Gly Thr Phe Ser Arg Cys Met Cys Thr Pro Ala Ala Arg Val
1               5                   10                  15

Phe Trp Asn Ala Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
            20                  25                  30
```

```
Ser Leu Leu Pro Pro Glu Leu Gln Asp Ile Asp Leu Ala Ala Ile Gly
        35                  40                  45

Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
65                  70                  75                  80

Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
                85                  90                  95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Thr
            100                 105                 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
        115                 120                 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
    130                 135                 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe
            180                 185                 190

Thr Asp Ser Ser Pro Asn Met Met Trp Thr Pro Glu Ser Asp Asp Ser
        195                 200                 205

Ala Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile
    210                 215                 220

Leu Ile Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp
225                 230                 235                 240

Glu Leu Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His
                245                 250                 255

Ser Gly Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys
            260                 265                 270

Trp Leu Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu
        275                 280                 285

Asp Tyr Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser
    290                 295                 300

Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val
305                 310                 315                 320

Ile Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln
                325                 330                 335

Ser Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe
            340                 345                 350

Val Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr
        355                 360                 365

Leu Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
    370                 375                 380


<210> SEQ ID NO 19
<211> LENGTH: 380
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 19

Met Ser Gly Thr Phe Ser Arg Cys Met Cys Thr Pro Ala Ala Arg Val
1               5                   10                  15

Phe Trp Asn Ala Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
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            20                  25                  30

Ser Leu Leu Pro Pro Glu Leu Gln Asp Ile Asp Leu Ala Ala Ile Gly
        35                  40                  45

Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
65                  70                  75                  80

Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
                85                  90                  95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Thr
            100                 105                 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
        115                 120                 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
    130                 135                 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe
            180                 185                 190

Thr Asp Ser Ser Pro Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala
        195                 200                 205

Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu
    210                 215                 220

Ile Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp Glu
225                 230                 235                 240

Leu Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser
                245                 250                 255

Gly Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp
            260                 265                 270

Leu Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp
        275                 280                 285

Tyr Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly
    290                 295                 300

Lys Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile
305                 310                 315                 320

Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser
                325                 330                 335

Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val
            340                 345                 350

Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu
        355                 360                 365

Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
    370                 375                 380


<210> SEQ ID NO 20
<211> LENGTH: 379
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 20

Met Ser Gly Thr Phe Ser Arg Cys Met Cys Thr Pro Ala Ala Arg Val
1               5                   10                  15
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Phe Trp Asn Ala Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
            20                  25                  30

Ser Leu Leu Pro Pro Glu Leu Gln Asp Ile Asp Leu Ala Ala Ile Gly
        35                  40                  45

Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
    50                  55                  60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
65                  70                  75                  80

Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
                85                  90                  95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Thr
            100                 105                 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
        115                 120                 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
    130                 135                 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145                 150                 155                 160

Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe
            180                 185                 190

Thr Asp Ser Ser Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp
        195                 200                 205

Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile
    210                 215                 220

Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp Glu Leu
225                 230                 235                 240

Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser Gly
                245                 250                 255

Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp Leu
            260                 265                 270

Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp Tyr
        275                 280                 285

Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly Lys
    290                 295                 300

Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile Asp
305                 310                 315                 320

Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser Trp
                325                 330                 335

Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val Arg
            340                 345                 350

Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu Arg
        355                 360                 365

Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
    370                 375


<210> SEQ ID NO 21
<211> LENGTH: 203
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 21

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15
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Pro Asn Gly Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp
            20                  25                  30

Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile
        35                  40                  45

Arg Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp Glu Leu
    50                  55                  60

Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser Gly
65                  70                  75                  80

Gly Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp Leu
                85                  90                  95

Ser Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp Tyr
            100                 105                 110

Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly Lys
        115                 120                 125

Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile Asp
    130                 135                 140

Pro Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser Trp
145                 150                 155                 160

Ile Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val Arg
                165                 170                 175

Leu Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu Arg
            180                 185                 190

Ile Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
        195                 200


<210> SEQ ID NO 22
<211> LENGTH: 202
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 22

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Asn Gly Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu
            20                  25                  30

Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg
        35                  40                  45

Ser Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp Glu Leu Ala
    50                  55                  60

Glu Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser Gly Gly
65                  70                  75                  80

Tyr Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp Leu Ser
                85                  90                  95

Cys Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp Tyr Leu
            100                 105                 110

Ala Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly Lys Tyr
        115                 120                 125

Leu Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile Asp Pro
    130                 135                 140

Asp Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser Trp Ile
145                 150                 155                 160

Arg His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val Arg Leu
                165                 170                 175

Thr Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu Arg Ile
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            180                 185                 190

Phe Arg Phe Gly Ala His Lys Trp Tyr Gly
        195                 200


<210> SEQ ID NO 23
<211> LENGTH: 201
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 23

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Asn Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu Glu
            20                  25                  30

Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45

Phe Pro Ala His His Pro Val Ser Leu Ala Asp Trp Glu Leu Ala Glu
    50                  55                  60

Ser Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser Gly Gly Tyr
65                  70                  75                  80

Leu Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp Leu Ser Cys
                85                  90                  95

Phe Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp Tyr Leu Ala
            100                 105                 110

Asn Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly Lys Tyr Leu
        115                 120                 125

Gln Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile Asp Pro Asp
    130                 135                 140

Gly Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser Trp Ile Arg
145                 150                 155                 160

His Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val Arg Leu Thr
                165                 170                 175

Ser Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu Arg Ile Phe
            180                 185                 190

Arg Phe Gly Ala His Lys Trp Tyr Gly
        195                 200


<210> SEQ ID NO 24
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 24

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu Glu Ala
            20                  25                  30

Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser Phe
        35                  40                  45

Pro Ala His His Pro Val Ser Leu Ala Asp Trp Glu Leu Ala Glu Ser
    50                  55                  60

Pro Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser Gly Gly Tyr Leu
65                  70                  75                  80

Val Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp Leu Ser Cys Phe
                85                  90                  95

Leu Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp Tyr Leu Ala Asn
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            100                 105                 110

Ala Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly Lys Tyr Leu Gln
        115                 120                 125

Arg Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile Asp Pro Asp Gly
    130                 135                 140

Pro Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser Trp Ile Arg His
145                 150                 155                 160

Leu Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val Arg Leu Thr Ser
                165                 170                 175

Leu Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu Arg Ile Phe Arg
            180                 185                 190

Phe Gly Ala His Lys Trp Tyr Gly
        195                 200


<210> SEQ ID NO 25
<211> LENGTH: 199
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 25

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu Glu Ala Leu
            20                  25                  30

Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser Phe Pro
        35                  40                  45

Ala His His Pro Val Ser Leu Ala Asp Trp Glu Leu Ala Glu Ser Pro
    50                  55                  60

Glu Asn Gly Phe Ser Phe Ser Thr Tyr His Ser Gly Gly Tyr Leu Val
65                  70                  75                  80

Gln Asn Pro Asp Val Phe Asp Ser Lys Cys Trp Leu Ser Cys Phe Leu
                85                  90                  95

Asp Gln Pro Ile Glu Val Arg Leu Tyr Glu Asp Tyr Leu Ala Asn Ala
            100                 105                 110

Phe Gly Tyr Gln Thr Lys Trp Gly Val Ser Gly Lys Tyr Leu Gln Arg
        115                 120                 125

Arg Leu Gln Val Asn Gly Ile Arg Ala Val Ile Asp Pro Asp Gly Pro
    130                 135                 140

Ile His Val Glu Ala Leu Ser Cys Pro Gln Ser Trp Ile Arg His Leu
145                 150                 155                 160

Thr Leu Asp Asp Asp Val Thr Pro Gly Phe Val Arg Leu Thr Ser Leu
                165                 170                 175

Arg Ile Val Pro Asn Thr Glu Pro Thr Thr Leu Arg Ile Phe Arg Phe
            180                 185                 190

Gly Ala His Lys Trp Tyr Gly
        195


<210> SEQ ID NO 26
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 26

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Asn Gly Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp
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            20                  25                  30

Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile
        35                  40                  45

Arg Ser
    50


<210> SEQ ID NO 27
<211> LENGTH: 49
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 27

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Asn Gly Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu
            20                  25                  30

Glu Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg
        35                  40                  45

Ser


<210> SEQ ID NO 28
<211> LENGTH: 48
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 28

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Asn Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu Glu
            20                  25                  30

Ala Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45


<210> SEQ ID NO 29
<211> LENGTH: 47
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 29

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Pro Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu Glu Ala
            20                  25                  30

Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45


<210> SEQ ID NO 30
<211> LENGTH: 46
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 30

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Asp Leu Glu Ala Leu
            20                  25                  30

Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45
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<210> SEQ ID NO 31
<211> LENGTH: 15110
<212> TYPE: DNA
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 31

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gtgatggttg cttaacttct cgacaccttc gtgaactcca agtttacgag cgtggctgca 600

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tatctgacca gccgttccct ggtgccaccc atgtgttgac gaactcgcct ttgcctcaac 720

aagcttgtcg gcagccgttc tgcccatttg aggaggctca ttctagcgtg tacaggtgga 780

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<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<221> NAME/KEY: MOD_RES
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 36

Ser Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Val Xaa Phe Xaa Asp Xaa Xaa
1 5 10 15

Xaa Xaa Gly Xaa Xaa Met Trp Xaa Xaa Xaa Ser Xaa Xaa Ser Xaa Xaa
20 25 30

Leu Glu Xaa Leu Pro Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa
35 40 45

Arg Ser
50

<210> SEQ ID NO 37
<211> LENGTH: 49
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
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<223> OTHER INFORMATION: Any amino acid
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<222> LOCATION: (40)..(45)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES

<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 37

Ser Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Val Xaa Phe Xaa Asp Xaa Xaa
1 5 10 15

Xaa Xaa Gly Xaa Met Trp Xaa Xaa Xaa Ser Xaa Xaa Ser Xaa Xaa Leu
20 25 30

Glu Xaa Leu Pro Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Arg
35 40 45

Ser

<210> SEQ ID NO 38
<211> LENGTH: 48
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
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<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(3)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
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<222> LOCATION: (46)..(46)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 38

Ser Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Val Xaa Phe Xaa Asp Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Met Trp Xaa Xaa Xaa Ser Xaa Xaa Ser Xaa Xaa Leu Glu
20 25 30

Xaa Leu Pro Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Arg Ser

35 40 45

<210> SEQ ID NO 39
<211> LENGTH: 47
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
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<223> OTHER INFORMATION: Any amino acid
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<222> LOCATION: (38)..(43)
<223> OTHER INFORMATION: Any amino acid
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<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 39

Ser Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Val Xaa Phe Xaa Asp Xaa Xaa
1 5 10 15

Xaa Xaa Met Trp Xaa Xaa Xaa Ser Xaa Xaa Ser Xaa Xaa Leu Glu Xaa
20 25 30

Leu Pro Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Arg Ser
35 40 45

<210> SEQ ID NO 40
<211> LENGTH: 46
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid
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<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 40

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Ser Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Val Xaa Phe Xaa Asp Xaa Xaa
1               5                   10                  15

Xaa Met Trp Xaa Xaa Xaa Ser Xaa Xaa Ser Xaa Xaa Leu Glu Xaa Leu
            20                  25                  30

Pro Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Arg Ser
        35                  40                  45
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<210> SEQ ID NO 41
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
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<222> LOCATION: (2)..(3)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
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<223> OTHER INFORMATION: Any amino acid
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<221> NAME/KEY: MOD_RES
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<223> OTHER INFORMATION: Any amino acid
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<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 41

Ser Xaa Xaa Tyr Xaa Xaa Xaa Xaa Xaa Val Xaa Phe Xaa Asp Xaa Xaa
1 5 10 15

Met Trp Xaa Xaa Xaa Ser Xaa Xaa Ser Xaa Xaa Leu Glu Xaa Leu Pro
20 25 30

Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Arg Ser
35 40 45

<210> SEQ ID NO 42
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<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
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<221> NAME/KEY: MOD_RES
<222> LOCATION: (41)..(45)

<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 42

Ala Xaa Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Xaa Val Ala Xaa
1 5 10 15

Xaa Xaa Xaa Ser Trp Ala Gly Gly Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Leu Xaa Leu Xaa Ala Xaa Xaa Xaa Xaa Xaa Ser
35 40 45

<210> SEQ ID NO 43
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(19)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(27)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)..(34)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (40)..(44)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 43

Ala Xaa Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Xaa Val Ala Xaa
1 5 10 15

Xaa Xaa Xaa Ser Trp Gly Gly Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Leu Xaa Leu Xaa Ala Xaa Xaa Xaa Xaa Xaa Ser
35 40 45

<210> SEQ ID NO 44
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(19)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)..(26)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(33)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (39)..(43)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 44

Ala Xaa Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Xaa Val Ala Xaa
1 5 10 15

Xaa Xaa Xaa Ser Gly Gly Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Leu Xaa Leu Xaa Ala Xaa Xaa Xaa Xaa Xaa Ser
35 40

<210> SEQ ID NO 45
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(19)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (22)..(25)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)..(32)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES

<222> LOCATION: (38)..(42)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 45

Ala Xaa Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Xaa Val Ala Xaa
1 5 10 15

Xaa Xaa Xaa Gly Gly Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Leu Xaa Leu Xaa Ala Xaa Xaa Xaa Xaa Xaa Ser
35 40

<210> SEQ ID NO 46
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(18)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (21)..(24)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (26)..(31)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (37)..(41)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 46

Ala Xaa Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Xaa Val Ala Xaa
1 5 10 15

Xaa Xaa Gly Gly Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Leu
20 25 30

Xaa Leu Xaa Ala Xaa Xaa Xaa Xaa Xaa Ser
35 40

<210> SEQ ID NO 47
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)

<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(23)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (25)..(30)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(40)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 47

Ala Xaa Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Xaa Val Ala Xaa
1 5 10 15

Xaa Gly Gly Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa
20 25 30

Leu Xaa Ala Xaa Xaa Xaa Xaa Xaa Ser
35 40

<210> SEQ ID NO 48
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 48

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1 5 10 15

Xaa Asn Gly Arg Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Xaa
20 25 30

Leu Glu Xaa Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile
35 40 45

Arg Ser
50

<210> SEQ ID NO 49
<211> LENGTH: 49
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:

<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 49

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1 5 10 15

Xaa Asn Gly Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Xaa Leu
20 25 30

Glu Xaa Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg
35 40 45

Ser

<210> SEQ ID NO 50
<211> LENGTH: 48
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 50

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1 5 10 15

Xaa Asn Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Xaa Leu Glu
20 25 30

Xaa Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
35 40 45

<210> SEQ ID NO 51
<211> LENGTH: 47
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 51

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1 5 10 15

Xaa Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Xaa Leu Glu Xaa
20 25 30

```
Leu Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45


<210> SEQ ID NO 52
<211> LENGTH: 46
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 52

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Ser
1               5                   10                  15

Met Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Xaa Leu Glu Xaa Leu
            20                  25                  30

Pro Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45


<210> SEQ ID NO 53
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 53

Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe Thr Asp Ser Met
1               5                   10                  15

Met Trp Thr Pro Glu Ser Asp Asp Ser Ala Xaa Leu Glu Xaa Leu Pro
            20                  25                  30

Pro Glu Leu Glu Arg Gln Val Glu Ile Leu Ile Arg Ser
        35                  40                  45


<210> SEQ ID NO 54
<211> LENGTH: 46
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Any amino acid
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 54

Ala Thr Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Tyr Val Ala Xaa
1 5 10 15

Xaa Lys Val Ser Trp Ala Gly Gly Xaa Glu Val Lys Phe Glu Xaa Val
20 25 30

Pro Xaa Glu Leu Lys Leu Xaa Ala Asn Arg Leu Xaa Thr Ser
35 40 45

<210> SEQ ID NO 55
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 55

Ala Thr Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Tyr Val Ala Xaa
1 5 10 15

Xaa Lys Val Ser Trp Gly Gly Xaa Glu Val Lys Phe Glu Xaa Val Pro
20 25 30

Xaa Glu Leu Lys Leu Xaa Ala Asn Arg Leu Xaa Thr Ser
35 40 45

<210> SEQ ID NO 56
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:

<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 56

Ala Thr Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Tyr Val Ala Xaa
1 5 10 15

Xaa Lys Val Ser Gly Gly Xaa Glu Val Lys Phe Glu Xaa Val Pro Xaa
20 25 30

Glu Leu Lys Leu Xaa Ala Asn Arg Leu Xaa Thr Ser
35 40

<210> SEQ ID NO 57
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (22)..(22)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 57

Ala Thr Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Tyr Val Ala Xaa
1 5 10 15

Xaa Lys Val Gly Gly Xaa Glu Val Lys Phe Glu Xaa Val Pro Xaa Glu
20 25 30

Leu Lys Leu Xaa Ala Asn Arg Leu Xaa Thr Ser
35 40

<210> SEQ ID NO 58
<211> LENGTH: 42

<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 58

Ala Thr Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Tyr Val Ala Xaa
1 5 10 15

Xaa Lys Gly Gly Xaa Glu Val Lys Phe Glu Xaa Val Pro Xaa Glu Leu
20 25 30

Lys Leu Xaa Ala Asn Arg Leu Xaa Thr Ser
35 40

<210> SEQ ID NO 59
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(9)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 59

Ala Thr Val Tyr Asp Ile Gly Xaa Xaa Ala Val Met Tyr Val Ala Xaa

1 5 10 15

Xaa Gly Gly Xaa Glu Val Lys Phe Glu Xaa Val Pro Xaa Glu Leu Lys
20 25 30

Leu Xaa Ala Asn Arg Leu Xaa Thr Ser
35 40

<210> SEQ ID NO 60
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(3)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 60

Ser Xaa Xaa Tyr
1

<210> SEQ ID NO 61
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 61

Ala Xaa Val Tyr
1

<210> SEQ ID NO 62
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 62

Ser Phe Pro
1

<210> SEQ ID NO 63
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 63

Arg Xaa Met Trp
1

<210> SEQ ID NO 64
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 64

Arg Gly Gly
1

<210> SEQ ID NO 65
<211> LENGTH: 3
<212> TYPE: PRT

<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 65

Arg Met Met
1

<210> SEQ ID NO 66
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 66

Arg Xaa Arg
1

<210> SEQ ID NO 67
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 67

Ala Pro Arg
1

<210> SEQ ID NO 68
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 68

Gly Arg Xaa Arg
1

<210> SEQ ID NO 69
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 69

Trp Ala Pro Arg
1

<210> SEQ ID NO 70
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 70

Trp Tyr Gly
1

<210> SEQ ID NO 71
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 71

Ala Gly Arg

1

<210> SEQ ID NO 72
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 72

Ala Ala Gly
1

<210> SEQ ID NO 73
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 73

Glu Cys Ala Met
1

<210> SEQ ID NO 74
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 74

Ala Xaa Val Tyr Asp
1 5

<210> SEQ ID NO 75
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 75

Glu Glu Ala His
1

<210> SEQ ID NO 76
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 76

Ser Xaa Val Tyr Arg
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<210> SEQ ID NO 77
<211> LENGTH: 2
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 77

Pro Arg
1

<210> SEQ ID NO 78
<211> LENGTH: 3

<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 78

Arg Pro Arg
1

<210> SEQ ID NO 79
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 79

Gly Arg Pro Arg
1

<210> SEQ ID NO 80
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 80

Asn Gly Arg Pro Arg
1 5

<210> SEQ ID NO 81
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 81

Pro Asn Gly Arg Pro Arg
1 5

<210> SEQ ID NO 82
<211> LENGTH: 389
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 82

Met Ser Gly Thr Phe Ser Arg Cys Met Cys Thr Pro Ala Ala Arg Val
1 5 10 15

Phe Trp Asn Ala Gly Gln Val Tyr Cys Thr Arg Cys Leu Ser Ala Arg
20 25 30

Ser Leu Leu Pro Pro Glu Leu Gln Asp Ile Asp Leu Ala Ala Ile Gly
35 40 45

Leu Phe Tyr Lys Pro Lys Asp Lys Leu His Trp Lys Val Pro Ile Gly
50 55 60

Ile Pro Gln Val Glu Cys Thr Pro Ser Gly Cys Cys Trp Leu Ser Gly
65 70 75 80

Ile Phe Pro Leu Ala Arg Met Thr Ser Gly Asn His Asn Phe Leu Gln
85 90 95

Arg Leu Val Lys Val Ala Asp Val Leu Tyr Arg Asp Gly Cys Leu Thr
100 105 110

Ser Arg His Leu Arg Glu Leu Gln Val Tyr Glu Arg Gly Cys Ser Trp
115 120 125

Tyr Pro Ile Thr Gly Pro Val Pro Gly Met Gly Leu Tyr Ala Asn Ser
130 135 140

Met His Val Ser Asp Gln Pro Phe Pro Gly Ala Thr His Val Leu Thr
145 150 155 160

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Asn Ser Pro Leu Pro Gln Gln Ala Cys Arg Gln Pro Phe Cys Pro Phe
                165                 170                 175

Glu Glu Ala His Ser Ser Val Tyr Arg Trp Lys Lys Phe Val Val Phe
            180                 185                 190

Thr Asp Ser Ser Pro Asn Gly Arg Pro Arg Met Met Trp Thr Pro Glu
        195                 200                 205

Ser Asp Asp Ser Ala Asp Leu Glu Ala Leu Pro Pro Glu Leu Glu Arg
    210                 215                 220

Gln Val Glu Ile Leu Ile Arg Ser Phe Pro Ala His His Pro Val Ser
225                 230                 235                 240

Leu Ala Asp Trp Glu Leu Ala Glu Ser Pro Glu Asn Gly Phe Ser Phe
                245                 250                 255

Ser Thr Tyr His Ser Gly Gly Tyr Leu Val Gln Asn Pro Asp Val Phe
            260                 265                 270

Asp Ser Lys Cys Trp Leu Ser Cys Phe Leu Asp Gln Pro Ile Glu Val
        275                 280                 285

Arg Leu Tyr Glu Asp Tyr Leu Ala Asn Ala Phe Gly Tyr Gln Thr Lys
    290                 295                 300

Trp Gly Val Ser Gly Lys Tyr Leu Gln Arg Arg Leu Gln Val Asn Gly
305                 310                 315                 320

Ile Arg Ala Val Ile Asp Pro Asp Gly Pro Ile His Val Glu Ala Leu
                325                 330                 335

Ser Cys Pro Gln Ser Trp Ile Arg His Leu Thr Leu Asp Asp Asp Val
            340                 345                 350

Thr Pro Gly Phe Val Arg Leu Thr Ser Leu Arg Ile Val Pro Asn Thr
        355                 360                 365

Glu Pro Thr Thr Leu Arg Ile Phe Arg Phe Gly Ala His Lys Trp Tyr
    370                 375                 380

Gly Ala Ala Gly Lys
385


<210> SEQ ID NO 83
<211> LENGTH: 203
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 83

Ala Asp Val Tyr Asp Ile Gly Arg Gly Ala Val Met Tyr Val Ala Gly
1               5                   10                  15

Gly Lys Val Ser Trp Ala Pro Arg Gly Gly Asn Glu Val Lys Phe Glu
            20                  25                  30

Pro Val Pro Lys Glu Leu Lys Leu Val Ala Asn Arg Leu His Thr Ser
        35                  40                  45

Phe Pro Pro His His Val Val Asp Met Ser Lys Phe Thr Phe Ile Thr
    50                  55                  60

Pro Gly Ser Gly Val Ser Met Arg Val Glu Tyr Gln Tyr Gly Cys Leu
65                  70                  75                  80

Pro Ala Asp Thr Val Pro Glu Gly Asn Cys Trp Trp Arg Leu Leu Asp
                85                  90                  95

Ser Leu Pro Pro Glu Val Gln Tyr Lys Glu Ile Arg His Ala Asn Gln
            100                 105                 110

Phe Gly Tyr Gln Thr Lys His Gly Val Pro Gly Lys Tyr Leu Gln Arg
        115                 120                 125

Arg Leu Gln Val Asn Gly Leu Arg Ala Val Thr Asp Thr His Gly Pro
    130                 135                 140
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Ile Val Ile Gln Tyr Phe Ser Val Lys Glu Ser Trp Ile Arg His Leu
145                 150                 155                 160

Lys Leu Val Glu Glu Pro Ser Leu Pro Gly Phe Glu Asp Leu Leu Arg
                165                 170                 175

Ile Arg Val Glu Pro Asn Thr Ser Pro Leu Ala Gly Lys Asp Glu Lys
            180                 185                 190

Ile Phe Arg Phe Gly Ser His Lys Trp Tyr Gly
        195                 200


<210> SEQ ID NO 84
<211> LENGTH: 203
<212> TYPE: PRT
<213> ORGANISM: Porcine reproductive and respiratory syndrome virus

<400> SEQUENCE: 84

Ala Thr Val Tyr Asp Ile Gly His Asp Ala Val Met Tyr Val Ala Glu
1               5                   10                  15

Arg Lys Val Ser Trp Ala Pro Arg Gly Gly Asp Glu Val Lys Phe Glu
            20                  25                  30

Ala Val Pro Gly Glu Leu Lys Leu Ile Ala Asn Arg Leu Arg Thr Ser
        35                  40                  45

Phe Pro Pro His His Thr Val Asp Met Ser Lys Phe Ala Phe Thr Ala
    50                  55                  60

Pro Gly Cys Gly Val Ser Met Arg Val Glu Arg Gln His Gly Cys Leu
65                  70                  75                  80

Pro Ala Asp Thr Val Pro Glu Gly Asn Cys Trp Trp Ser Leu Phe Asp
                85                  90                  95

Leu Leu Pro Leu Glu Val Gln Asn Lys Glu Ile Arg His Ala Asn Gln
            100                 105                 110

Phe Gly Tyr Gln Thr Lys His Gly Val Ser Gly Lys Tyr Leu Gln Arg
        115                 120                 125

Arg Leu Gln Val Asn Gly Leu Arg Ala Val Thr Asp Leu Asn Gly Pro
    130                 135                 140

Ile Val Val Gln Tyr Phe Ser Val Lys Glu Ser Trp Ile Arg His Leu
145                 150                 155                 160

Lys Leu Ala Gly Glu Pro Ser Tyr Ser Gly Phe Glu Asp Leu Leu Arg
                165                 170                 175

Ile Arg Val Glu Pro Asn Thr Ser Pro Leu Ala Asp Lys Glu Glu Lys
            180                 185                 190

Ile Phe Arg Phe Gly Ser His Lys Trp Tyr Gly
        195                 200
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The invention claimed is:

1. A replication-competent Porcine Reproductive and Respiratory Syndrome (PRRS) virus comprising a deletion of at least three consecutive nucleotide triplets in the gene sequence encoding the N terminal domain (NTD) of the nsp1β subunit of the nsp1 protein of said virus, wherein the NTD starts with the N-terminus of nsp1β of amino acid sequence SXXY (SEQ ID NO: 60) and ends with the serine (S) residue within the amino acid sequence SFP (SEQ ID NO: 62), wherein said deletion of three consecutive nucleotide triplets comprises the first encoded arginine residue (R) located at least 21 amino acid residues located in the C-terminal direction from the NTD amino acid residue of nsp1β and two amino acid residues flanking said R residue in the N-terminal direction, and wherein the modified PRRS virus induces production and secretion of interferon type I by a cell infected with said virus.

2. The PRRS virus according to claim **1**, wherein said modification comprises a deletion of three consecutive nucleotide triplets coding for the amino acid sequence RXR (SEQ ID NO: 66) of the nsp1β subunit, or wherein said mutation comprises a deletion of four consecutive nucleotide triplets coding for the amino acid residues GRXR (SEQ ID NO: 68) of the nsp1β subunit, wherein X is a genetically encoded amino acid residue.

3. The PRRS virus according to claim **1**, wherein said PPRS virus has increased sensitivity to interferon type I.

4. The PRRS virus according to claim **1**, wherein said PRRS virus is an attenuated PRRS virus.

5. The PRRS virus according to claim **1**, wherein said PPRS virus is a genotype I.

6. The PRRS virus according to claim **1**, wherein said interferon type I is Interferon-α, Interferon-β or combinations thereof.

7. The PRRS virus according to claim **1**, wherein said cell is a mammalian cell, and wherein said mammalian cell is a cell of a primary or secondary cell line or a host cell.

8. The PRRS virus according to claim **7**, wherein said mammalian cell is a porcine cell or a simian cell.

9. The PRRS virus according to claim **8**, wherein said porcine cell is a porcine macrophage.

10. The PRRS virus according to claim **8**, wherein said simian cell is a MA-104 or a MARC-145 cell.

11. A method for the treatment of Porcine Reproductive and Respiratory Syndrome comprising administering an effective amount of the PRRS virus of claim **1** to a swine, pig, piglet or a sow in need of said treatment.

12. A polynucleotide comprising the genome of the PRRS virus according to claim **1**.

13. A DNA Vector comprising a copy of the polynucleotide of claim **12**.

14. A virus particle comprising the polynucleotide of claim **12** or **13**.

15. A cell comprising the polynucleotide of claim **12** or the DNA-vector of claim **13**.

16. A method of preparing a PRRS virus composition comprising the cultivation of the PRRS virus according to claim **1** in cell culture.

17. A method for the detection of interferon type I, or of mRNA coding for interferon type I by the cell infected with the modified PRRS virus of claim **1**, wherein the interferon type I and/or the mRNA coding for interferon type I is detected by a bioassay, wherein said bioassay is preferably selected from the group consisting of ELISA, PCR, GLISA, IFA, biosensoric measurement, Surface Plasmon Resonance (SPR) measurement, selective media, lateral flow, biochip measurement, immunomagnetic separation, electrochemiluminescence, chromogenic media, immunodiffusion, DNA hybridization, staining, colorimetric detection, luminescence, and combinations thereof.

18. An immunogenic composition comprising the PRRS virus according to claim **1**.

19. The immunogenic composition according to claim **18**, comprising an amount of 10^1 to 10^7 viral particles per dose.

20. The immunogenic composition according to claim **18**, comprising an amount of 10^3 to 10^6 particles per dose.

21. The immunogenic composition according to claim **18**, comprising an amount of 10^4 to 10^6 particles per dose.

22. The immunogenic composition according to claim **18**, comprising an amount of said PRRS virus which is equivalent to a virus titre of at least about 10^3 $TCID_{50}$/mL per dose.

23. The immunogenic composition according to claim **18**, comprising an amount of said PRRS virus which is equivalent to a virus titre of between 10^3 to 10^5 $TCID_{50}$/mL per dose.

24. The immunogenic composition according to claim **18**, further comprising one or more pharmaceutically acceptable carriers or excipients.

25. The immunogenic composition according to claim **24**, wherein said one or more pharmaceutically acceptable carriers or excipients are selected from the group consisting of solvents, dispersion media, adjuvants, stabilizing agents, diluents, preservatives, antibacterial and antifungal agents, isotonic agents, and adsorption delaying agents.

26. A method for inducing an immune response against PRRSV comprising administering an effective amount of the immunogenic composition of claim **18** to an animal in need thereof.

27. The method of claim **26**, wherein the immunogenic composition is administered in a single dose or in two doses.

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